NOV 22 1920

BULLETIN

OF

THE JOHNS HOPKINS HOSPITAL

(THE PUBLICATION OF THE MEDICAL SCHOOL AND HOSPITAL)

Vol. XXXI—No. 357] BALTIMORE, NOVEMBER, 1920 [Price, 50 Cents

CONTENTS

	PAGE
The Effect of Diphtheria Antitoxin in Preventing Lodgment and Growth of the Diphtheria Bacillus in the Nasal Passages of Animals. By J. Gelien, W. L. Moss, and C. G. Guthrie	381
Diphtheria Bacillus Carriers. Second Communication. By C. G. Guthrie, J. Gelien, and W. L. Moss	388
The Treatment of Neurosyphilis by the Intraspinal Route. With the Report of a Clinical Study of a Series of Cases Treated from the Point of View of Increased Permeability of the Meninges. By Albert Keidel and Joseph Earle Moore	404
Mononuclear Leucocytosis in Reaction to Acute Infections. ("Infectious Mononucleosis".) (Illustrated.) By Thomas P. Sprunt and Frank A. Evans	410
Pneumococcus Type I Vegetative Endocarditis. Report of a Case Following an Attack of Lobar Pneumonia. (Illustrated.) By Henry M. Thomas, Jr., and Dwight O'Hara	417
Notes on New Books	420
Books Received	421

Entered as Second-Class Matter at the Baltimore, Maryland, Postoffice
Acceptance for mailing at special rate of postage provided for in Section 1103, Act of October 3, 1917. Authorized on July 3, 1918.

THE EFFECT OF DIPHTHERIA ANTITOXIN IN PREVENTING LODGMENT AND GROWTH OF THE DIPHTHERIA BACILLUS IN THE NASAL PASSAGES OF ANIMALS

By J. Gelien, W. L. Moss and C. G. Guthrie, M. D.

(From the Research Laboratory, Phipps Tuberculosis Dispensary, Johns Hopkins Hospital)

The value of antitoxin as a curative agent in the treatment of diphtheria has been proven beyond all doubt. Its efficacy, also, in the prophylaxis of the disease is so well known as to need no comment, except that the immunity conferred by it is relative, passive, and exerted over a short but variable period. On the other hand, the desirability of its prophylactic use is, perhaps, questionable and a subject which merits further consideration. Whether used as a curative or preventive agent, its action depends upon its ability to neutralize the circulating toxin elaborated by the diphtheria bacillus. This action is purely antitoxic, not bactericidal, but apparently this fact is not infrequently overlooked, although supported by abundant experimental and clinical evidence. Diphtheria bacilli may persist in the nose and throat of an individual for weeks and even months after all clinical manifestations of the disease have disappeared, despite the oft repeated injection of antitoxin subcutaneously. Likewise, the local use of antitoxin in the pharynx and nares is without effect, other than the mechanical cleansing which might be accomplished as well, perhaps, with salt solution. Doubtless negative cultures are sometimes obtained after local treatment with antitoxin, but *post hoc* is not necessarily *propter hoc*, and we have seen cases that resisted it for weeks, although administered by firm believers in this method of eradication. It has been our observation that Klebs-Loeffler bacilli may disappear from the nose and throat of those recovering from diphtheria following the employment of various other local measures or may persist in spite of any or all such medication. On the other hand, they may vanish spontaneously without assistance from the physician. Such observations, together with a considerable series of unpublished experiments on animals with regard to this point, have led us to question the value of the forms of local treatment so far proposed for this purpose. If one may judge from experiments *in vitro*, there is no reason to suppose that antitoxin has any virtue as a local agent since the diphtheria bacillus grows luxuriantly in it.

Another rather important aspect of the antitoxin question is usually overlooked or dismissed with a few words. This concerns its effect in preventing the lodgment and growth of the diphtheria bacillus in individuals receiving prophylactic injections. In order to throw some light on this point, the

animal experiments which form the basis of this report were undertaken.

Object. *To determine whether antitoxin administered subcutaneously will prevent the subsequent lodgment and growth of diphtheria bacilli in the naso-pharynx.*

Procedure. Guinea-pigs, rabbits and cats were the animals employed and the general plan of procedure was as follows. Preliminary cultures were made on all the animals to show that they were free from diphtheria bacilli at the beginning of the experiments. The animals used in each experiment were divided into two groups, one of which received antitoxin subcutaneously, the other group serving as a control, without antitoxin. Subsequently both groups were exposed equally to infection with diphtheria bacilli. In one series of experiments this exposure consisted in the introduction of diphtheria bacilli into the naso-pharynx by means of a swab. In others an attempt was made to imitate more nearly natural conditions. This consisted in caging both groups—(that which had received antitoxin and that which had not)—with a "carrier" animal. At the outset it was intended to follow the animals throughout the investigation by means of throat cultures, but we soon found that nasal cultures were more practicable and more satisfactory. Tiny swabs were made by winding a small wisp of cotton about the coarser and stiffer end of pig bristles. After a little practice it was found quite simple to introduce a swab by way of the nostril into the posterior nares. Cultures were made on Loeffler's blood serum and examined after 15 or 20 hours in the thermostat. Diphtheria bacilli were isolated from a large percentage of the positive cultures and the result of the primary examinations confirmed. Preliminary cultures showed that all of the animals used were free from diphtheria organisms before inoculation. As will be indicated when the experiments are taken up in detail, certain of the animals were subjected to nasal inoculation with *B. diphtheriæ* from time to time. These inoculations were made by introducing into the posterior nares a swab which had been soaked in a thick, opaque suspension of diphtheria bacilli. Two strains of organisms were used which were obtained from the throats of school children during the course of a previous investigation. Both were typical in morphology and cultural characteristics, but one (1157) was virulent and the other (1032) was avirulent.

After preliminary nasal culture of all the animals they were divided into groups of 10, with the exception of those used in Experiments VII and VIII, which consisted in each instance of a cat with five kittens. Each group was kept in a separate floor cage, sufficiently large to avoid overcrowding and removed as far as was possible from the other groups. One half of the animals in each group received diphtheria antitoxin beneath the skin of the abdomen, 250 units being the individual dose. This was followed next day by nasal inoculation of all animals in Series A (Exp. I, II and III) and by the introduction into each group of Series B (Exp. IV, V, VI, VII and VIII) of a "carrier" animal which that day received artificial nasal inoculation with diphtheria bacilli. Nasal cultures were then taken at two-day intervals. It soon became apparent that the initial inoculation with diphtheria bacilli had been insufficient or ineffectual, as in some of the groups no positive cultures were found for six days thereafter. For this reason the injection of antitoxin was repeated and in the afternoon of the same day the animals were re-inoculated. On this occasion, thicker suspensions of bacteria were used and the infected swabs were allowed to remain in the nose for a longer time than at the primary inoculation. The nasal cultures at intervals of two days were resumed and a much higher percentage of positive results obtained.

A few words with regard to the fate of the 70 animals used in this work may not be inappropriate here. None of them developed signs or symptoms of diphtheria, and those that died showed no evidence of this disease. The guinea-pigs and rabbits remained healthy, with one exception (R. 219, Exp. V), and were in a thriving condition at the conclusion of the experiments. Among the cats, however, there was a high mortality, owing to the prevalence of distemper * and the difficulty in keeping these animals healthy in confinement.

The list of experiments in detail, with the results obtained is shown in Series A and B.

* "Distemper" is merely used as a convenient term for the disease characterized by sore eyes, snuffles and bronchopneumonia.

SERIES A

EXPERIMENT I.—Nasal cultures from ten guinea-pigs. All having artificial nasal inoculation with avirulent diphtheria bacilli. Five having previously received diphtheria antitoxin subcutaneously. Five not having previously received diphtheria antitoxin subcutaneously

Animal number	Preliminary culture July 1	Antitoxin subcutaneously July 1	Nasal inoculation with *B. diphtheriæ* (1032) July 2	Result of culture 1 July 4	Result of culture 2 July 6	Antitoxin subcutaneously July 6 A. M.	Nasal inoculation with *B. diphtheriæ* (1032) July 6 P. M.	Result of culture 3 July 8	Result of culture 4 July 10
G.-P. 12....	0	250 units	Yes	0	0	250 units	Yes	+	0
13....	0	" "	"	0	0	" "	"	+	0
14....	0	" "	"	0	0	" "	"	0	0
15....	0	" "	"	0	0	" "	"	0	0
16....	0	" "	"	0	0	" "	"	+	0
17....	0	None	"	0	0	None	"	0	0
18....	0	"	"	0	0	"	"	+	0
19....	0	"	"	0	0	"	"	0	0
20....	0	"	"	0	0	"	"	+	0
21....	0	"	"	0	0	"	"	0	0

SERIES A—CONTINUED

EXPERIMENT II.—Nasal cultures from ten rabbits. All having artificial nasal inoculation with virulent diphtheria bacilli. Five having previously received diphtheria antitoxin subcutaneously. Five not having previously received diphtheria antitoxin subcutaneously

Animal number	Preliminary culture June 27	Antitoxin subcutaneously June 27	Nasal inoculation with *B. diphtheriæ* (1157) June 28	Result of culture 1 June 30	Result of culture 2 July 2	Result of culture 3 July 4	Result of culture 4 July 6	Antitoxin subcutaneously July 6	Nasal inoculation with *B. diphtheriæ* (1157) July 6	Result of culture 5 July 8	Result of culture 6 July 10
R. 210.....	0	250 units	Yes	0	0	0	+	250 units	Yes	+	0
230.....	0	" "	"	0	0	0	0	" "	"	0	0
225.....	0	" "	"	0	0	0	0	" "	"	0	0
235.....	0	" "	"	0	0	0	0	" "	"	0	0
220.....	0	" "	"	0	0	0	+	" "	"	0	0
234.....	0	None	"	0	0	0	0	None	"	0	0
214.....	0	"	"	0	0	0	0	"	"	+	0
223.....	0	"	"	0	0	0	0	"	"	0	0
236.....	0	"	"	0	0	0	0	"	"	+	0
226.....	0	"	"	0	0	0	+	"	"	+	0

EXPERIMENT III.—Nasal cultures from ten cats. All having artificial nasal inoculation with avirulent diphtheria bacilli. Five having previously received diphtheria antitoxin subcutaneously. Five not having previously received diphtheria antitoxin subcutaneously

Animal number	Preliminary culture June 28	Antitoxin subcutaneously June 28	Nasal inoculation with *B. diphtheriæ* (1032) June 29	Result of culture 1 July 1	Result of culture 2 July 3	Result of culture 3 July 5	Antitoxin subcutaneously July 6 A. M.	Nasal inoculation with *B. diphtheriæ* (1032) July 6 P. M.	Result of culture 4 July 7	Result of culture 5 July 9	Result o culture 6 July 11
C. 1....	0	250 units	Yes	0	0	0	250 units	Yes	+	0	0
2....	0	" "	"	+	0	0	" "	"	0	0	0
3....	0	" "	"	+	0	0	" "	"	0	0	0
4....	0	" "	"	0	0	0	" "	"	0	0	+
5....	0	" "	"	0	0	0	" "	"	+	0	0
6....	0	None	"	0	0	0	None	"	+	0	+
7....	0	"	"	0	0	0	"	"	+	Dead	..
8....	0	"	"	0	0	0	"	"	+	0	+
9....	0	"	"	0	0	0	"	"	0	0	+
10....	0	"	"	Dead	..	..	..	..	..	..	..
34	0	"	"	+	0	0	"	"	+	+	+

C. 10 died June 30. Autopsy negative. C. 4 and C. 5 killed July 13. Autopsy negative except for pus in nose and inflammation of intestines. C. 7 died July 8. Intestinal symptoms. C. 34 substituted for C. 10, July 1.

SERIES B

EXPERIMENT IV.—Nasal cultures from 11 guinea-pigs. One having artificial inoculation with virulent diphtheria bacilli. Ten not having artificial nasal inoculation with virulent diphtheria bacilli. Five having previously received diphtheria antitoxin subcutaneously. Five not having previously received diphtheria antitoxin subcutaneously

Animal number	Preliminary culture June 22	Antitoxin subcutaneously June 28	Nasal inoculation with *B. diphtheriæ* (1157) June 29	Result of culture 1 July 1	Result of culture 2 July 3	Result of culture 3 July 5	Antitoxin subcutaneously July 6 A. M.	Nasal inoculation with *B. diphtheriæ* (1157) July 6 P. M.	Result of culture 4 July 7	Result of culture 5 July 9
G.-P. 1....	0	250 units	No	0	0	+	250 units	No	0	+
2....	0	" "	"	+	0	0	" "	"	0	+
3....	0	" "	"	0	0	0	" "	"	+	+
4....	0	" "	"	0	0	+	" "	"	0	0
5....	0	" "	"	0	0	0	" "	"	+	0
6....	0	None	"	0	0	+	None	"	0	0
7....	0	"	"	+	0	+	"	"	+	0
8....	0	"	"	+	0	+	"	"	+	+
9....	0	"	"	+	0	+	"	"	+	0
10....	0	"	"	0	0	0	"	"	0	0
11....	0	"	Yes	+	0	0	"	Yes	+	+

EXPERIMENT V.—Nasal cultures from 11 rabbits. One having artificial nasal inoculation with avirulent diphtheria bacilli. Ten not having artificial nasal inoculation with avirulent diphtheria bacilli. Five having previously received diphtheria antitoxin subcutaneously. Five not having previously received diphtheria antitoxin subcutaneously

Animal number	Preliminary culture June 27	Antitoxin subcutaneously June 27	Nasal inoculation with *B. diphtheriæ* (1032) June 28	Result of culture 1 June 30	Result of culture 2 July 2	Result of culture 3 July 4	Result of culture 4 July 6	Antitoxin subcutaneously July 6 A. M.	Nasal inoculation with *B. diphtheriæ* (1032) July 6 P. M.	Result of culture 5 July 8	Result of culture 6 July 10
R. 219	0	250 units	No	0	0	0	0	250 units	No	+	Dead
233	0	" "	"	+	0	0	0	" "	"	0	0
231	0	" "	"	0	0	0	0	" "	"	+	0
224	0	" "	"	0	0	0	0	" "	"	+	0
222	0	" "	"	0	0	0	0	" "	"	0	0
237	0	None	"	0	0	0	0	None	"	+	0
226	0	"	"	9	0	0	0	"	"	0	0
227	0	"	"	0	0	0	0	"	"	0	0
128	0	"	"	0	0	0	0	"	"	0	0
216	0	"	"	0	0	0	0	"	"	..	..
228	0	"	Yes	0	0	0	0	"	Yes	+	0

R. 219 died July 10. Autopsy: Plastic pleurisy right side, plastic peritonitis.

SERIES B—CONTINUED

EXPERIMENT VI.—Nasal cultures from 11 cats. One having artificial nasal inoculation with virulent diphtheria bacilli. Ten not having artificial nasal inoculation with virulent diphtheria bacilli. Five having previously received diphtheria antitoxin subcutaneously

Animal number	Preliminary culture June 29	Antitoxin subcutaneously June 29	Nasal inoculation with *B. diphtheriæ* (1157) June 30	Result of culture July 2	Result of culture July 4	Result of culture July 6	Antitoxin subcutaneously July 6 A. M.	Nasal inoculation with *B. diphtheriæ* (1157) July 6 P. M.	Result of culture July 8	Result of culture July 10
C. 23.....	0	250 units	No	0	0	0	250 units	No	0	0
24.....	0	" "	"	Dead	....	....	.....	....	....	....
25.....	0	" "	"	0	0	0	250 units	No	0	0
26.....	0	" "	"	0	0	0	Dead	....	....	....
27.....	0	" "	"	0	0	0	250 units	No	+	0
56.....	0	" "	"	0	0	0	" "	"	+	0
46.....	0	.....	"	.....	....	....	" "	"	0	0
28.....	0	None	"	0	0	0	None	"	0	0
29.....	0	"	"	0	0	0	"	"	0	0
30.....	0	"	"	Dead	....	....	.....	....	....	....
31.....	0	"	"	0	0	0	None	No	0	0
32.....	0	"	"	0	0	0	"	"	0	0
42.....	0	"	"	0	0	0	"	"	0	0
33.....	0	"	Yes	0	0	0	"	Yes	+	0

C. 24 died July 2. Autopsy negative. C. 26 died July 6. C. 30 died July 1. Autopsy negative. Intestinal symptoms. C. 42 substituted for C. 30, C. 56 substituted for C. 24 and C. 46 substituted for C. 26.

EXPERIMENT VII.—Nasal cultures from six cats (mother and five kittens). Mother having artificial nasal inoculation with virulent diphtheria bacilli. Kittens not having artificial nasal inoculation with virulent diphtheria bacilli. Two kittens having previously received diphtheria antitoxin subcutaneously. Three kittens not having previously received diphtheria antitoxin subcutaneously

Animal number	Preliminary culture June 28	Antitoxin subcutaneously June 28	Nasal inoculation with *B. diphtheriæ* (1157) June 29	Result of culture 1 July 1	Result of culture 2 July 3	Result of culture 3 July 5	Antitoxin subcutaneously July 6 A. M.	Nasal inoculation with *B. diphtheriæ* (1157) July 6 P. M.	Result of culture 4 July 7	Result of culture 5 July 9	Result of culture 6 July 11
C. 12....	0	250 units	No	0	0	0	250 units	No	+	+	+
13....	0	" "	"	0	0	0	" "	"	+	+	+
14....	0	None	"	0	0	0	None	"	0	+	+
15....	0	"	"	0	0	0	"	"	0	+	0
16....	0	"	"	0	0	0	"	"	+	+	+
11....	0	"	Yes	0	0	0	..	....	..	..	..
54....	0	....	....	..	..	..	"	Yes	+	+	+

C. 12, 13, 14, 15, 16 } kittens.

{ C. 11, mother cat escaped July 6.
C. 54, female cat (lactating) substituted for C. 11, July 6.

SERIES B—CONTINUED

EXPERIMENT VIII.—Nasal cultures from six cats (mother and five kittens). Mother having artificial nasal inoculation with avirulent diphtheria bacilli. Kittens not having artificial nasal inoculation with avirulent diphtheria bacilli. Three kittens having previously received diphtheria antitoxin subcutaneously. Two kittens not having previously received diphtheria antitoxin subcutaneously

Animal number	Preliminary culture June 28	Antitoxin subcutaneously June 28	Nasal inoculation with *B. diphtheriæ* (1032) June 29	Result of culture 1 July 1	Result of culture 2 July 3	Result of culture 3 July 5
C. 18.....	0	250 units	No	0	0	0
19.....	0	" "	"	0	Dead	....
20.....	0	" "	"	+	0	+
21.....	0	None	"	0	Dead	....
22.....	0	"	"	0	0	0
17.....	0	"	Yes	0	0	0

C. 18, 19, 20, 21, 22 } kittens. { C. 17, mother cat. C. 19 died July 2. Autopsy. Sore eyes, pneumonia. C. 21, died July 1. Autopsy. Sore eyes, pneumonia.

ANALYSIS OF RESULTS OF EXPERIMENTS I TO VIII *

		Number of animals				Total number of cultures			
		With antitoxin		Without antitoxin		Animals with antitoxin		Animals without antitoxin	
		Sometime pos. cult.	Always neg. cult.	Sometime pos. cult.	Always neg. cult.	Total pos. cult.	Total neg. cult.	Total pos. cult.	Total neg. cult.
Series A.....	Experiment I, organism avirulent (1032)..	3	2	2	3	3	17	2	18
	Experiment II, organism virulent (1157)...	2	3	3	2	3	27	4	26
	Experiment III, organism avirulent (1032)..	5	0	5	0	5	25	10	18
	Total.....	10	5	10	5	11	69	16	62
Series B.....	Experiment IV, organism virulent (1157)...	5	0	4	1	8	17	11	14
	Experiment V, organism avirulent (1032)..	4	1	1	4	4	25	1	26
	Experiment VI, organism virulent (1157)...	2	3	0	5	2	23	0	25
	Experiment VII, organism avirulent (1032)..	2	0	3	0	6	6	6	12
	Experiment VIII, organism virulent (1157)...	1	2	0	2	2	5	0	7
	Total.....	14	6	8	12	22	76	18	84
Series A and B..	Experiments I–VIII. Total.....	24	11	18	17	33	145	34	146
Series A and B..	Organism virulent (1157) Exp. II, IV, VI, VIII.	11	6	10	8	19	73	21	77
	Organism avirulent (1032) Exp. I, III, V, VII.	13	5	8	9	14	72	13	69
	Total.....	24	11	18	17	33	145	34	146
Series A and B..	Guinea-pigs. Experiments I and IV.....	8	2	6	4	11	34	13	32
	Rabbits. Experiments II and V.....	6	4	4	6	7	52	5	52
	Cats. Experiments III, VI, VII and VIII ...	10	5	8	7	15	59	16	62
	Total.....	24	11	18	17	33	145	34	146

* This table does not include the preliminary cultures which were made on all the animals, nor the results of cultures on the "carriers" in Series B, *vid.*, Exp. IV, G. P. 11; Exp. V, R. 228; Exp. VI, C. 33; Exp. VII, C. 11 and C. 54; Exp. VIII, C. 17.

To this may be appended, for the sake of comparison, the cultural results obtained with a series of 40 animals used in other experiments. The animals were arranged in groups of 10 and, after preliminary cultures, all were inoculated in the same manner and with the same strains of bacteria as in the foregoing experiments. They, also, were cultured at two-day intervals and after each culture one half the animals in each group were sprayed in the nose with killed cultures of *Staphylococcus aureus* or *B. pyocyaneus*. Later, living cultures of these organisms were used but no beneficial effect, inhibitive or otherwise, could be noted as a result of the spraying. The results of the cultures are merely given to serve as a comparison with the figures given in the analyses of results of Experiments I to VIII.

SHOWING RESULTS OF EXPERIMENTS IX TO XII

Experiment number	Number and kind of animal	*B. diphtheriæ* used for inoculation	Organism used in spray treatment	Number of animals		Number of cultures	
				+	0	+	0
IX	10 rabbits	Avirulent (1032)	Pyocyaneus	7	3	10	33
X	10 cats	Virulent (1157)	Pyocyaneus	1	9	1	27
XI	10 rabbits	Avirulent (1032)	Aureus	3	7	4	16
XII	10 guinea-pigs	Virulent (1157)	Aureus	6	4	7	21
				17	23	22	97

SHOWING COMBINED RESULTS OF EXPERIMENTS I TO XII

	Number of annimals				Number of cultures			
	+	0	Total	%+	+	0	Total	%+
Experiments I to VIII (Series A and B)	42	28	70	60%	67	291	358	19%
Experiments IX to XII (Aureus and Pyocyaneus)	17	23	40	43%	22	97	119	18%
Total	59	51	110	54%	89	388	477	19%
Guinea-pigs. Experiments I, IV and XII	20	10	30	66%	31	87	118	26%
Rabbits. Experiments II, V, IX and XI	20	20	40	50%	26	153	179	15%
Cats. Experiments III, VI, VII, VIII and X	19	21	40	48%	32	148	180	18%
Total	59	51	110	54%	89	388	477	19%

Comment. Certain conditions in these experiments with animals are quite different from those which obtain in human beings, notably the frequency with which the carrier state occurs spontaneously and the ease with which it may be produced experimentally.

In a large series of human beings including both children and adults, we found that a single examination revealed an incidence of diphtheria bacillus carriers of about 3.55 per cent. A second examination practically doubled the number of carriers discovered, while a third examination still further increased the original number. Among the 72 animals which form the basis of these experiments as well as the 40 additional animals referred to in the body of the paper none showed diphtheria bacilli at the beginning of the work.

We have been able to induce the carrier state in man experimentally both with virulent and with non-virulent diphtheria bacilli, not with regularity, it is true, but in a considerable proportion of a small series of individuals.* In guinea-pigs, rabbits and cats, however, we found the carrier state difficult to produce and generally very transient if it occurred at all. The number of diphtheria bacilli present in the positive cultures, moreover, was very small as compared with the total number of organisms of various kinds which developed. This is a condition of affairs quite different from that commonly observed in cultures from human carriers and raises the question as to whether the diphtheria bacilli had actually multiplied or merely persisted in the nasal passages of these animals. On the basis of experience derived from work with these and other animals of the same kinds, we believe that those animals showing positive cultures at the last recorded observation would probably have become negative in a few days.

* A detailed account of this work will appear in a later paper.

It is evident that the period covered by these examinations was too short. Observations over a longer time would have served, in all probability, to render the results more striking and clear cut. Despite these drawbacks, some facts seem apparent from the 358 cultures on 70 animals.

Summary. (1) The production of nasal infection or infestation of cats, rabbits and guinea-pigs with *B. diphtheriæ* was quite inconstant even when the organisms were introduced directly into the nose.

(2) A somewhat higher percentage of animals showed positive cultures among those directly inoculated than among those merely exposed to a "carrier" (Series A, 66 per cent; Series B, 55 per cent). A much greater discrepancy would not have been surprising.

(3) Cats and rabbits became infected with about the same frequency (C., 48 per cent; R., 50 per cent) and the incidence of positive cultures was also much the same (C., 18 per cent; R., 15 per cent). Among the guinea-pigs, 66 per cent developed positive cultures and 26 per cent of the total number of cultures taken showed Klebs-Loeffler bacilli.

(4) The duration of infection was usually quite short but may have been variable in this respect, as some animals still harbored diphtheria organisms at the end of the experiments.

(5) The health of the animals was apparently unaffected by the mere presence of the bacilli in the nose.

(6) The occurrence and duration of infection were independent of the virulence of the strain of organisms used for inoculation and (7) were wholly unaffected by the previous administration of antitoxin.

CONCLUSION

The subcutaneous administration of antitoxin does not prevent the lodgment and growth of *B. diphtheriæ* in the nasal passage of cats, guinea-pigs and rabbits.

DIPHTHERIA BACILLUS CARRIERS

SECOND COMMUNICATION*

By C. G. Guthrie, J. Gelien and W. L. Moss

(From the Division of Clinical Pathology of the Medical Clinic, The Johns Hopkins Hospital and University)

PART I

The following brief summary gives the main facts brought out in our first communication, published in the Transactions of the Fifteenth International Congress on Hygiene and Demography, 1912, IV, 156.

Incidence of diphtheria bacillus carriers among presumably healthy persons as shown by a single examination of the throat.

A single throat culture from each of 1217 school children revealed diphtheria bacilli in 44 instances, 3.61 per cent. A single throat culture from each of 1290 individuals in the city at large, most diverse as to age, sex, race and social position, showed diphtheria bacilli in 45 cases, 3.48 per cent. These two groups together make a total of 2507 individuals in the city of Baltimore during the spring of 1911, 89 of whom gave a positive throat culture, 3.55 per cent.

* This investigation was made by authority of the Department of Health of Baltimore City, and it is a pleasure to make grateful acknowledgment of the hearty co-operation and valuable assistance of Dr. Jas. Bosley, Commissioner of Health, Dr. C. Hampson Jones, Assistant Commissioner of Health, Drs. R. A. Urquhart and I. R. Page, school physicians, and Mrs. H. E. Knorr, school nurse.

The cultures and examinations of the throats were made in all instances by Drs. Urquhart and Page. Mrs. Knorr visited each "carrier" in his or her home and made the most thorough and painstaking inquiry which forms, in large part, the basis of our report on the relation of the carrier to the community.

Persistence of diphtheria bacilli in the throats of persons who gave a positive culture. Forty-six of the school children who gave a positive culture at the first or second examination were re-examined after a lapse of 1½ to 3 months, and 10, or 21.74 per cent, again gave positive cultures.

Virulence of the diphtheria bacilli present in the throats of children having positive cultures. Diphtheria bacilli were isolated from 33 of the children having positive cultures and their virulence tested. Six, or 18.18 per cent, were found to be virulent.

Relation of diphtheria bacillus carriers to the community. The most important and striking feature of the investigation was the previous and subsequent history and the relation to the community with reference to clinical diphtheria of 49 school children having positive cultures. Of these 49 diphtheria bacillus carriers a history of previous clinical diphtheria could be obtained in only 3 (three, four and five years previously), a positive history of previous exposure was obtained in 3 (three, five and seven years previously), and a doubtful history of exposure, four years previously, in one. Not one of the 49 carriers subsequently, during the period of observation, developed clinical diphtheria, and a most careful investigation failed to reveal a single case of clinical diphtheria developing among any of the associates of these 49 carriers.

In discussing the results of this investigation, we pointed out that a single examination of any group of persons is not sufficient to determine the true incidence of carriers and it follows, of course, that a single re-examination is not sufficient to determine the question of persistence.

In order to throw more light on some of the questions raised in our first report and to extend our observations to cover some additional problems, we have undertaken a second investigation.*

OBJECT

1. To determine the persistence of *B. diphtheriæ* in the throats of persons having positive cultures but not suffering from clinical diphtheria.

2. To determine the virulence or non-virulence of the diphtheria bacilli present in the throats of such persons.

3. To determine whether the diphtheria bacilli growing in the throats of such persons may undergo a change in virulence; that is, whether a virulent one may become avirulent or an avirulent organism acquire virulence while growing in the throat of a carrier.

4. To determine whether any relation exists between the presence of diphtheria bacilli and pathological throat conditions other than clinical diphtheria.

5. To determine by history and observation whether:

(a) Any of the carriers investigated have at any previous time had clinical diphtheria.

(b) Any of them develop clinical diphtheria during the period they are under observation.

(c) Any of them have ever been exposed to a case of clinical diphtheria.

(d) Any one in contact with the carriers investigated develops clinical diphtheria.

PLAN FOR CARRYING OUT THE ABOVE INVESTIGATION

1. Fifty diphtheria bacillus carriers are to be selected and throat cultures made on them at intervals of two weeks for a period of three months.

2. At the time of each culture any obviously pathological condition of the throat, such as hypertrophied and infected tonsils, pharyngitis, etc., is to be noted and the temperature of the child recorded.*

3. Each time a positive culture is obtained the diphtheria bacillus is to be isolated in pure state, tested for virulence and its cultural, morphological and tinctorial characteristics studied.

In order to secure 50 carriers for the purpose of this investigation a single throat culture was made on each of 800 children in School V (February 12, 13, 14 and 15, 1912). This was the school which had yielded the highest percentage of positive cultures in the course of our work in 1911. The name, age, sex, class and home address of the child and objective condition of the throat at the time of making the culture were recorded. From the children having positive cultures at this examination 50 were selected for repeated cultures according to the plan outlined above and at the end of three months a reculture was made of the original 800 children and pathological conditions of the throat again noted. Moreover, temperature observations were made on 431 of these children at the time of this examination.

The observations made on the 800 children, from whom the 50 carriers were selected, furnished data on some points not specifically set forth as the object of this investigation, but which it seems worth while to include in the report.

An analysis and summary of the results of the first examination of 800 children in School V, made February, 1912, is contained in Table I.

Examination of Table I shows that among 800 children 85 were found to have positive throat cultures, 10.62 per cent.

There were 426 males and 374 females. The incidence of positive cultures in these two groups was practically the same, 10.56 per cent among the males and 10.69 per cent among the females.

There were 221 children under eight years of age with an incidence of 11.31 per cent of positive cultures and 579

* In the various studies on diphtheria bacillus carriers and in the animal experiments in connection with them which we have made it has been necessary to use a large amount of diphtheria antitoxin. Antitoxin for this purpose was generously furnished us free of cost by the Lederle Laboratory and we desire to acknowledge with appreciation $150.00 worth of antitoxin received from this source.

* Great care was taken in this investigation to prevent any possibility of carrying infection from one child to another. In making the throat examinations a separate wooden tongue depressor was used for each child and afterwards burned. In taking the temperatures the thermometers were disinfected by being placed for five minutes in a 1-1000 solution of mercury bichloride each time before a temperature was taken.

children over eight years old with 10.36 per cent of positive cultures.

TABLE I

FIRST EXAMINATION OF 800 CHILDREN, SCHOOL V, FEBRUARY, 1912. ANALYZED WITH REFERENCE TO AGE, SEX, POSITIVE CULTURES AND PATHOLOGICAL THROATS

	Pos. cultures		Path. throats	
	Number	Per cent	Number	Per cent
800 children 4–17 years old...	85	10.62	211	26.37
426 males.....	45	10.56	127	29.81
374 females.....	40	10.69	84	22.46
221 children under 8 years....	25	11.31	75	33.93
579 children over 8 years.....	60	10.36	136	23.48
110 males under 8 years.....	11	10.00	48	43.63
111 females under 8 years....	14	12.61	27	24.32
316 males over 8 years.....	34	10.75	79	25.00
263 females over 8 years.....	26	9.88	57	21.67

Males under eight years had a slightly smaller percentage of positive cultures than did the females under eight years: 10 per cent for males as compared with 12.61 per cent for females. Males over eight years, on the other hand, had a slightly higher percentage of positive cultures than did females over eight years of age; 10.75 per cent as compared with 9.88 per cent.

The above percentages are remarkable, not for their variation, but for their very great uniformity and they indicate that, in the children examined, there was practically no difference in the incidence of positive cultures in the various groups considered.

When we come to analyze the above table for pathological throat conditions we find wide variations between the sexes, at different ages, etc. The total number of throats noted as pathological in the 800 children examined is 211, or 26.37 per cent. More of these occur in males (29.81 per cent) than in females (22.46 per cent). More occur in children under eight years old (33.93 per cent) than in children over eight years old (23.48 per cent). Males under eight years old have the highest incidence of any group (43.63 per cent). Females under eight years have an incidence of 24.32 per cent. Males over eight years, 25 per cent. Females over eight years, 21.67 per cent.

We wish next to analyze the relationship which exists between pathological conditions of the throat and the occurrence of positive cultures and to determine, if possible, whether this relation is a causal one; and if a causal one, which is cause and which effect (see Table II).

If we compare in the various groups the incidence of positive cultures in pathological throats with the incidence of positive cultures in normal throats (Table II) we find:

	Per cent
In 211 children with pathological throats 25 pos. cultures..	11.84
In 589 children with normal throats 60 pos. cultures.....	10.18

TABLE II

COMPARING THE INCIDENCE OF POSITIVE CULTURES IN CHILDREN HAVING PATHOLOGICAL THROATS AND IN THOSE HAVING NORMAL THROATS

	Positive cultures	
	Number	Per cent
211 children with path. throats.....	25	11.84
589 children with normal throats.....	60	10.18
127 males with path. throats.....	13	10.23
299 males with normal throats.....	32	10.70
84 females with path. throats.....	12	14.28
290 females with normal throats.....	28	9.65
75 children under 8 years path. throats.....	12	16.00
146 children under 8 years normal throats.....	13	8.90
136 children over 8 years path. throats.....	13	9.55
443 children over 8 years normal throats.....	47	10.85
48 males under 8 years path. throats.....	5	10.41
62 males under 8 years normal throats.....	6	9.67
27 females under 8 years path. throats.....	7	25.92
84 females under 8 years normal throats.....	7	8.33
79 males over 8 years path. throats.....	8	10.12
237 males over 8 years normal throats.....	26	10.97
57 females over 8 years path. throats.....	5	8.75
206 females over 8 years normal throats.....	21	10.19

Further analysis shows that the incidence of positive cultures is higher in females with pathological throats than in females with normal throats (14.28 per cent in the former and 9.65 per cent in the latter). The incidence of positive cultures is higher in children under eight years old with pathological throats than in children under eight years old with normal throats (16 per cent in the former and 8.90 per cent in the latter). The incidence of positive cultures is higher in females under eight years old with pathological throats than in females under eight years old with normal throats (25.92 per cent in the former and 8.33 per cent in the latter).

If on the other hand we compare, in the various groups the incidence of pathological throat conditions in children who have positive cultures with the incidence of pathological throat conditions in children who have negative cultures (Table III) we find:

	Per cent
In 85 children with pos. cultures, 25 path. throats	29.41
In 715 children with neg. cultures, 186 path. throats	26.01

Further analysis shows that the incidence of pathological throats is higher in females with positive cultures than in females with negative cultures.

The incidence of pathological throats is higher in children under eight years old with positive cultures than it is in children under eight years old with negative cultures.

The incidence of pathological throats is higher in females under eight years old with positive cultures than it is in females under eight years old with negative cultures. From

TABLE III

COMPARING THE INCIDENCE OF PATHOLOGICAL THROATS IN CHILDREN HAVING POSITIVE CULTURES AND THOSE HAVING NEGATIVE CULTURES

	Pathological throats	
	Number	Per cent
85 children with positive cultures	25	29.41
715 children with negative cultures	186	26.01
45 males with positive cultures	13	28.88
381 males with negative cultures	114	29.92
40 females with positive cultures	12	30.00
334 females with negative cultures	72	21.55
25 children under 8 years positive cultures	12	48.00
196 children under 8 years negative cultures	63	32.14
60 children over 8 years positive cultures	13	21.66
519 children over 8 years negative cultures	123	23.69
11 males under 8 years positive cultures	5	45.45
99 males under 8 years negative cultures	43	43.43
14 females under 8 years positive cultures	7	50.00
97 females under 8 years negative cultures	20	20.62
34 males over 8 years positive cultures	8	23.53
282 males over 8 years negative cultures	71	25.17
26 females over 8 years positive cultures	5	19.23
237 females over 8 years negative cultures	52	21.94

the above analysis it appears that in the series of cases under discussion positive cultures were found with about the same frequency in pathological throats as in normal throats, 11.84 per cent as compared with 10.18 per cent, and that pathological throats were found but slightly more frequently in children who had positive cultures than in those with negative cultures, 29.41 per cent as compared with 26.01 per cent. We think it would be unsafe to draw conclusions from differences so slight as the above.

Up to this point in the analysis no attention has been paid to the virulence of the cultures. Of the 85 positive cultures 64 were tested for virulence and 8, or 12.50 per cent, found virulent. Of the eight virulent cultures, three were found in males and five in females. Three occurred in children under eight years of age and five in children over eight years. Five occurred in children with apparently normal throats and three in children with evidently pathological throats.

Beginning May 13, 1912, three months after the first culture, the same 800 children were re-examined. The results have been analyzed and summarized in Table IV.

Examination of Table IV shows that at this time there were 69 positive cultures among the 800 children, 8.62 per cent. The percentage among males and females was again practically the same (8.45 per cent and 8.82 per cent). Children under eight years old gave an incidence of 9.50 per cent, as compared with 8.29 per cent in children over eight years old. Males under eight years old gave 8.18 per cent of

TABLE IV

SECOND EXAMINATION OF 800 CHILDREN, SCHOOL V, MAY, 1912. ANALYZED WITH REFERENCE TO AGE, SEX, POSITIVE CULTURES AND PATHOLOGICAL THROATS

	Pos. cultures		Path. throats	
	Number	Per cent	Number	Per cent
800 children 4–17 years	69	8.62	107	13.37
426 males	36	8.45	66	15.49
374 females	33	8.82	41	10.96
221 children under 8 years	21	9.50	35	15.83
579 children over 8 years	48	8.29	72	12.43
110 males under 8 years	9	8.18	19	17.27
111 females under 8 years	12	10.81	16	14.41
316 males over 8 years	27	8.54	47	14.87
263 females over 8 years	21	7.98	25	9.50

positive cultures as compared with 10.81 per cent in females under eight years old. Males over eight years old gave 8.54 per cent of positive cultures and females over eight years gave 7.98 per cent of positive cultures. As was the case in the previous examinations, so in this examination the results seem remarkable for their lack of variation between different age and sex groups.

It will be noticed that at the time of the last examination the total incidence of positive cultures was somewhat less than at the first examination and that the number of pathological throats was only about half as great as at the first examination. These results were probably influenced by the seasons at which the two examinations were made, the first occurring in February, the second in May. Notwithstanding the marked reduction in the incidence of pathological throat conditions at the time of the last examination, the relative distribution in the different age and sex groups is almost exactly the same as at the first examination; thus the incidence of pathological throats is higher in males (15.49 per cent) than in females (10.96 per cent), higher in children under eight years old (15.83 per cent) than in children over eight years old (12.43 per cent), and reaches its maximum in males under eight years old (17.27 per cent).

If we compare in the various groups the incidence of positive cultures in pathological throats with the incidence of positive cultures in normal throats (Table V) we find as follows:

	Per cent
In 107 children with path. throats, 15 positive cultures	14.01
In 693 children with normal throats, 54 positive cultures	7.93

The incidence of positive cultures is higher in females with pathological throats, 26.82 per cent, than in females with normal throats, 6.60 per cent. It is higher in children under eight years old with pathological throats, 22.85 per cent, than in children under eight years old with normal throats, 6.98 per cent. It is much higher in females under eight years old

TABLE V

COMPARING THE INCIDENCE OF POSITIVE CULTURES IN CHILDREN HAVING PATHOLOGICAL THROATS AND THOSE HAVING NORMAL THROATS

	Positive cultures	
	Number	Per cent
107 children with path. throats	15	14.01
693 children with normal throats	54	7.93
66 males with path. throats	4	6.06
360 males with normal throats	32	8.88
41 females with path. throats	11	26.82
333 females with normal throats	22	6.60
35 children under 8 years with path. throats	8	22.85
186 children under 8 years with normal throats	13	6.98
72 children over 8 years with path. throats	7	9.86
507 children over 8 years with normal throats	41	8.08
19 males under 8 years with path. throats	0	0.00
91 males under 8 years with normal throats	9	9.89
16 females under 8 years with path. throats	8	50.00
95 females under 8 years with normal throats	4	4.21
47 males over 8 years with path. throats	4	8.51
269 males over 8 years with normal throats	23	8.55
25 females over 8 years with path. throats	3	12.00
238 females over 8 years with normal throats	18	7.56

with pathological throats, 50 per cent, than in females under eight years old with normal throats, 4.21 per cent.

If on the other hand we compare the incidence of the pathological throat conditions occurring in children who have positive cultures with the incidence of pathological throat conditions in children who have negative cultures (Table VI) we find:

	Per cent
In 69 children with pos. cultures, 15 with path. throats	21.73
In 731 children with neg. cultures, 92 with path. throats	12.58

As was the case in the analysis of the first examination so in this one there was a higher incidence of pathological throats in the females with positive cultures than in females with negative cultures (33.33 per cent as compared with 8.79 per cent). The incidence of pathological throats was higher in children under eight years of age with positive cultures than in children under eight years with negative cultures (38.09 per cent as compared with 13.50 per cent). The incidence of pathological throats is much higher in females under eight years old with positive cultures than in females under eight years old with negative cultures (66.66 per cent as compared with 8.08 per cent).

Analyzed from the standpoint of the virulent cultures the following results are obtained: Of the 69 positive cultures 41 were tested and three found virulent (7.31 per cent). None

TABLE VI

COMPARING THE INCIDENCE OF PATHOLOGICAL THROATS IN CHILDREN HAVING POSITIVE CULTURES AND THOSE HAVING NEGATIVE CULTURES

	Pathological throats	
	Number	Per cent
69 children with positive cultures	15	21.73
731 children with negative cultures	92	12.58
36 males with positive cultures	4	11.11
390 males with negative cultures	62	15.89
33 females with positive cultures	11	33.33
341 females with negative cultures	30	8.79
21 children under 8 years with positive cultures	8	38.09
200 children under 8 years with negative cultures	27	13.50
48 children over 8 years with positive cultures	7	14.58
531 children over 8 years with negative cultures	65	12.24
9 males under 8 years with positive cultures	0	00.00
101 males under 8 years with negative cultures	19	18.81
12 females under 8 years with positive cultures	8	66.66
99 females under 8 years with negative cultures	8	8.08
27 males over 8 years with positive cultures	4	14.81
289 males over 8 years with negative cultures	43	14.87
21 females over 8 years with positive cultures	3	14.28
242 females over 8 years with negative cultures	22	9.09

of the three virulent cultures occurred in throats which were evidently pathological.

As previously stated, 85 positive cultures were found among 800 children at the first examination and three months later a second examination of the same 800 children yielded 69 positive cultures. Comparison of the two lists of positive cultures revealed the striking fact that only 10 of the children gave positive cultures at both examinations. That is to say, 75 of the children who gave positive cultures at the first examination gave negative cultures at the second examination and 59 of the children who gave positive cultures at the second examination gave negative cultures at the time of the first examination. Does this mean that 75 of the children with positive cultures at the time of the first examination had succeeded in getting rid of the diphtheria bacilli which they had been carrying in their throats and that 59 children who gave negative cultures at the time of the first examination subsequently became infested? We think that such conclusions are not justified. We pointed out in our first communication that a single culture from each of a group of individuals will yield a number of positive cultures far below the real incidence of carriers and that two examinations will nearly double the number of positive cultures obtained. We think it safe to assume that many of the 85 children who gave positive cultures at the first examination still carried diphtheria bacilli in their throats at the time of the second examination

and that a majority of the 69 children who gave positive cultures at the second examination probably had diphtheria bacilli at the time of the first examination.*

The case is somewhat different with regard to the observations of pathological throat conditions, a considerable number of which were acute and were present at one or the other examination but not at both. It seems to us justifiable to combine the positive cultures found on the two examinations and analyze the figures thus obtained, but no such combination is permissible in the case of the observations on pathological throats.

The figures obtained by combining the positive cultures found on the two examinations appear in Table VII.

TABLE VII

RESULTS OF FIRST AND SECOND EXAMINATION OF 800 CHILDREN, SCHOOL V, COMBINED AND ANALYZED WITH REFERENCE TO AGE, SEX AND POSITIVE CULTURES

	Positive cultures	
	Number	Per cent
800 children 4–17 years	144	18.00
426 males	75	17.60
374 females	69	18.44
221 children under 8 years	40	18.09
579 children over 8 years	104	17.96
110 males under 8 years	17	15.45
111 females under 8 years	23	20.72
316 males over 8 years	58	18.35
263 females over 8 years	46	17.49

Table VII shows that among the 800 children examined there were 144, or 18 per cent, who at one time or another showed a positive throat culture. Males and females showed practically the same percentage of positive cultures (17.60 per cent for males and 18.44 per cent for females). Children under eight years and those over eight years old showed practically the same percentage (18.09 and 17.96 per cent). As was the case in the analysis of the results of the two examinations separately, so in the analysis of the combined results, females under eight years of age showed the highest percentage of positive cultures of any group, 20.72 per cent. Males under eight years old gave 15.45 per cent positive cultures. Males over eight years old, 18.35 per cent, and females over eight years old, 17.49 per cent positive cultures.

Virulence tests were done on the cultures from 99 children and eleven were found virulent, 11.11 per cent. Of the 11 virulent cultures five occurred in males and six in females. Four occurred in children under eight years and seven in children over eight years old. Seven occurred in children with apparently normal throats and four in children with evidently pathological throats.

* We have a considerable amount of evidence in support of this view which will be presented in a subsequent paper.

As previously mentioned, temperature observations were made on 431 of the children at the time of the last examination.

We wish to analyze the results to see if any relationship can be shown to exist between the temperature, pathological throat conditions and positive cultures.

For this purpose we shall compare the incidence of temperature elevations:

(a) In children with pathological throat conditions and in those whose throats are normal.

(b) In children with positive cultures and those with negative cultures.

(c) In children with positive cultures and pathological throats with those having positive cultures and normal throats.

(d) In children with negative cultures and pathological throat conditions with those having negative cultures and normal throats.

TABLE VIII

	Total	Temp. up to 99°	Temp. over 99°
Pathological throats	78	57—73.07%	21—26.92%
Normal throats	353	262—74.22%	91—25.77%
Positive cultures	39	34—87.17%	5—12.82%
Negative cultures	392	285—72.70%	107—27.29%

Table VIII shows the temperature relations between children having pathological throats and those having normal throats and the relation between those having positive cultures and those having negative cultures.

Of the 431 children whose temperature was recorded 78 had pathological throats and 353 had normal throats. The percentage of children whose temperature was above 99° F. was practically equal in the two groups, 26.92 per cent among those with pathological throats and 25.77 per cent among those with normal throats. There were 39 children with positive cultures and 392 with negative cultures. The percentage with an elevation of temperature above 99° F. was higher among the children with negative cultures, 27.29 per cent, than among those with positive cultures, 12.82 per cent.

Table IX shows the relations to temperature elevations of the following four groups:

(1) Positive cultures and pathological throats.
(2) Positive cultures and normal throats.
(3) Negative cultures and pathological throats.
(4) Negative cultures and normal throats.

TABLE IX

		Temp. up to 99°	Temp. over 99°
39 positive cultures	11 path. throats	8—72.72%	3—27.27%
	28 normal throats	26—92.85%	2— 7.14%
392 negative cultures	67 path. throats	49—73.13%	18—26.86%
	325 normal throats	236—72.61%	89—27.38%

The percentage of children with an elevation of temperature above 99° F. is higher among those with positive cultures

and pathological throats, 27.27 per cent, than among those with positive cultures and normal throats, 7.14 per cent, but is about equal to that of children with negative cultures and pathological throats, 26.86 per cent, and of the group with negative cultures and normal throats, 27.38 per cent.

If we regard as carriers those who gave a positive culture at either examination and compare the temperature observations on that group with those who did not give a positive culture at either examination, we find that temperature elevations above 99° occurred with about the same relative frequency in the group who twice gave negative cultures, 25.87 per cent, as in the carrier group, 26.37 per cent.

Table X shows the percentage of temperature elevations in the four groups mentioned above.

TABLE X

		Temp. up to 99°	Temp. over 99°
91 at some time positive cultures	19 path. throats..	13—68.42%	6—31.58%
	72 normal throats	54—75.00%	18—25.00%
340 twice negative cultures	60 path. throats	45—75.00%	15—25.00%
	280 normal throats	207—73.92%	73—26.07%

From this table it appears that temperature elevations above 99° F. occurred slightly more frequently in the group with positive cultures and pathological throats than in the other three groups, temperature elevations in the other three groups occurring with practically the same frequency.

Summary, Part I

A single throat culture from each of 800 children attending one of the public schools of Baltimore, in February, 1912, revealed *B. diphtheriæ* in 85, 10.62 per cent.

A re-examination of the same 800 children three months later gave 69 positive cultures, 8.62 per cent.

The number of children yielding positive cultures at either one or the other examination was 144, or 18 per cent.

The incidence of positive cultures was practically the same among males and females, and in the different age and sex groups.

At the time of the first examination 211 of the 800 children were noted as having pathological conditions of the throat, 26.37 per cent.

At the time of the second examination (three months later and in milder weather) 107 children were noted as having pathological conditions of the throat, 13.37 per cent.

Pathological throats were more frequent among males than among females, more frequent in children under eight years of age than among children over eight years of age and reached their maximum frequency in males under eight years of age.

At the time of the first examination there were found among the 211 children having pathological throats, 25 positive cultures, 11.84 per cent, and among the 589 children with normal throats, 60 positive cultures, 10.18 per cent.

At the time of the re-examination of the 800 children there were found among the 107 children having pathological throats 15 positive cultures, 14.01 per cent, and among the 693 children with normal throats, 54 positive cultures, 7.93 per cent. At both examinations the highest percentage of positive cultures found in any age and sex group was in females under eight years old having pathological throats. We refrain from drawing any general conclusion from this latter fact owing to the smallness of the group.

At the first examination 25 children were found to have pathological throats among the 85 who gave positive cultures, 29.41 per cent, and 186 children had pathological throats among the 715 who gave negative cultures, 26.01 per cent.

At the second examination 15 children had pathological throats among the 69 who gave positive cultures, 21.73 per cent, and 92 children had pathological throats among the 731 who gave negative cultures, 12.58 per cent. At both examinations the highest incidence of pathological throats found in any age and sex group was in females under eight years having positive cultures. In this case also we refrain from drawing general conclusions from such small numbers.

Virulence tests were done on the cultures from 99 children and 11 were found virulent, 11.11 per cent. It would not be safe to draw conclusions from the distribution of these 11 virulent cultures in the various age and sex groups.

Temperature observations were made on 431 of the children at the time of the last examination. The results have been analyzed to see whether any relationship can be shown to exist between temperature elevations, pathological throat conditions and positive cultures.

Temperature elevations above 99° F. occurred with about the same frequency in the following three groups: (a) Children with pathological throats, (b) those with normal throats and (c) those with negative cultures. They occurred much less frequently among the children with positive cultures.

Analyzed from the standpoint of any influence which the various combinations of cultures and throat condition might have on the temperature it was found that the incidence of temperature elevations was about equal in the following three groups:

(a) Positive culture and pathological throat.
(b) Negative culture and pathological throat.
(c) Negative culture and normal throat.

The incidence of temperature elevations was considerably less in the group with positive cultures and normal throats.

If we regard as carriers those children who gave at either examination a positive culture, we find that the highest incidence of temperature elevations occurring in any group was among carriers who had pathological throat conditions.

PART II

1. *To determine the persistence of B. diphtheriæ in the throats of persons having positive cultures but not suffering from clinical diphtheria.*

When this investigation was planned we assumed that the persistence of diphtheria bacilli in the throats of carriers could

be determined by selecting a number of individuals having diphtheria bacilli in their throats and making cultures at intervals to determine when they ceased to be carriers. There were evident fallacies in this assumption. In the first place, we had no means of knowing how long diphtheria bacilli had already persisted in the throats of the children selected for this investigation at the time our observations were begun. In the second place, in case a child has a positive culture followed by one or more negative cultures and then another positive culture we cannot exclude the possibility that the bacilli originally present have been gotten rid of and that re-infestation has taken place. It must be conceded that this latter possibility may exist even in the cases in which a positive culture was obtained at every examination; dis-infestation and re-infestation may have taken place in the two weeks interval between the examinations. In the third place, we have a series of observations on a small group of carriers under more carefully controlled conditions which show that daily examinations may be negative over a period of several days followed by positive cultures for a number of consecutive examinations. Care must therefore be exercised in attempting to draw conclusions regarding persistence of the bacilli from the six re-examinations of the 50 children whose cultures were positive at the time of the first examination and who were selected as carriers for further study.

The first column at the extreme left of Table XI contains the serial numbers of the 50 children selected for repeated examinations. The second column contains their serial number in the list of 800 children from which the 50 were selected. The column at the extreme right of the table shows the number of times a positive culture was obtained from each child.

Under each examination are four columns: the first shows whether the culture was positive or negative, the second indicates the virulence or avirulence of the culture isolated, the third gives the temperatures of the children at the time of each examination and the fourth column shows whether a pathological condition of the throat was noted.

\+ indicates positive culture.
0 indicates negative culture.
a indicates an *avirulent* culture.
v indicates a *virulent* culture.
P indicates a pathological condition of the throat.

Table XI gives the results of cultures on these 50 children, results of the virulence tests on the bacilli isolated together with the temperature and throat observations. In the six re-examinations (297 cultures) 85 positive cultures were obtained (28.62 per cent). These were distributed as follows:

13	cases	pos.	cults.	found	on	re-exam.	0	times =	0	pos. cults.
16	"	"	"	"	"	"	1	time =	16	" "
8	"	"	"	"	"	"	2	times =	16	" "
7	"	"	"	"	"	"	3	" =	21	" "
0	"	"	"	"	"	"	4	" =	0	" "
4	"	"	"	"	"	"	5	" =	20	" "
2	"	"	"	"	"	"	6	" =	12	" "
50	cases			297	cultures				85	pos. cults. (28.62 per cent)

Of the 50 children who had positive cultures at the time of the first examination, only 29 yielded positive cultures two weeks later at the time of the second examination. At the third examination the number of positive cultures had fallen to 15 and at the fourth, fifth, sixth and seventh examinations the number of positive cultures was 11, 12, 12 and 6 respectively.

We think that this progressive decline in the number of positive cultures indicates that the diphtheria bacilli had actually disappeared from the throats of some of the children, but we do not think that the inference can be drawn that all but six of the 50 who at the first examination had positive cultures had gotten rid of their diphtheria bacilli. We have shown previously that the number of positive cultures revealed by two examinations of a group of people will be nearly twice the number revealed by a single examination. More than two examinations would probably still further increase the number of positive cultures found. We may therefore infer that diphtheria bacilli persisted in the throats of considerably more than six of the 50 carriers for a period of six weeks.

2. *To determine the virulence or non-virulence of the diphtheria bacilli present in the throats of carriers.*

Virulence tests were performed on organisms isolated from all except three of the 50 carriers (Nos. 65, 174, 376). Virulent organisms were found in only six of the 47 carriers thus examined (12.76 per cent).

Of the 135 positive cultures obtained from the 50 carriers selected for repeated examination virulence tests were performed on 110; 12, or 10.90 per cent, were found virulent.

3. *To determine whether the diphtheria bacilli growing in the throats of carriers may undergo a change in virulence; that is, whether a virulent one may become avirulent or an avirulent organism acquire virulence while growing in the throat of a carrier.*

Thirty of the carriers in the above series had virulence tests performed on organisms isolated from two or more separate cultures taken at intervals of two weeks or longer, and in only three cases were virulent organisms found at one time and avirulent organisms at another. The results in these three cases were as follows: Case 25 on the first, fourth, fifth, sixth and seventh examination yielded avirulent cultures and on the second and third examination yielded virulent cultures. Case 131 yielded virulent cultures on the first, second and third examination and avirulent cultures on the fourth, fifth and sixth examination. Case 182 yielded virulent cultures on the first and fifth examination and an avirulent culture on the sixth examination. It is, perhaps, needless to say that in these instances in which irregularity occurred in the results of the virulence test on successive cultures, the tests were repeated to check up a possible slip or technical error. In each instance the original results were confirmed.

There are three possible explanations for the above observations:

1. The bacilli may undergo a change during residence in the throat, acquiring or losing virulence.

TABLE XI

		1st exam.				2d exam.				3d exam.				4th exam.				5th exam.				6th exam.				7th exam.				
1	4	+	a	....	P	0	..	98.2	..	+	a	100.2	..	+	a	100 0	P	+	a	99.8	..	0	..	99.8	..	0	..	100.1	..	4
2	24	+	a	....	..	+	a	98.6	P	0	..	99.4	P	0	..	98.2	P	0	..	100.1	P	0	..	99.8	..	0	..	99.9	..	2
3	25	+	a	....	..	+	v	98.0	..	+	v	99.4	..	+	a	98.8	P	+	a	99.0	P	+	a	99.4	..	+	a	99.0	P	7
4	48	+	a	....	..	+	a	98.8	P	+	a	99.8	P	0	..	99.2	..	0	..	99.8	..	+	a	99.0	P	0	..	98.6	..	4
5	50	+	a	....	..	+	..	98.6	..	+	..	99.6	P	0	..	98.7	P	+	a	99.6	P	0	..	99.0	..	0	..	99.2	..	4
6	55	+	a	....	..	0	..	98.2	..	0	..	99.2	..	0	..	99.8	..	0	..	99.6	..	0	..	98.8	..	0	..	99.0	..	1
7	65	+	..	....	..	0	..	97.8	P	0	..	98.0	..	0	..	98.4	P	0	..	100.3	..	0	..	98.6	..	0	..	97.6	P	1
8	67	+	v	....	..	0	..	98.0	P	0	..	100.0	..	+	..	98.6	P	0	..	99.8	..	0	..	99.8	..	0	..	98.8	..	2
9	70	+	a	....	..	+	..	98.6	..	0	..	99.0	P	0	..	98.4	P	0	..	99.8	P	0	..	99.4	..	0	..	99.0	P	2
10	75	+	a	....	..	+	a	97.6	..	0	..	98.0	P	+	a	98.6	..	0	..	99.0	..	0	..	98.6	..	0	..	98.6	..	3
11	122	+	a	....	P	+	..	100.1	P	0	..	98.4	P	0	..	98.2	P	0	..	98.6	P	0	..	98.6	..	+	a	99.2	P	3
12	126	+	a	....	..	0	..	98.8	P	+	a	99.4	..	+	a	98.6	..	+	a	100.3	..	+	..	99.2	..	+	..	99.0	..	6
13	130	+	a	....	..	0	..	100.1	P	0	..	....	..	0	..	99.8	..	0	..	98.6	P	0	..	98.2	..	..	..	....	..	1
14	131	+	v	....	..	+	v	99.0	P	+	v	99.6	..	+	a	98.2	P	+	a	100.4	P	+	a	98.6	P	0	..	99.2	..	6
15	134	+	a	....	..	+	a	99.6	P	+	..	100.6	P	0	..	99.6	P	0	..	100.0	..	0	..	99.8	..	0	..	99.8	..	3
16	147	+	a	....	..	+	a	99.2	..	+	..	99.6	..	0	..	99.0	..	+	a	100.6	..	0	..	99.6	..	0	..	98.6	..	4
17	148	+	v	....	P	0	..	101.0	P	0	..	98.2	P	0	..	98.6	..	0	..	99.4	P	0	..	98.8	P	0	..	99.6	..	1
18	149	+	a	....	..	+	a	98.9	..	+	a	100.2	..	+	a	99.6	P	+	a	99.4	..	+	a	99.0	..	+	a	98.8	..	7
19	150	+	a	....	P	+	a	97.8	P	0	..	98.4	..	0	..	98.8	P	0	..	99.4	P	0	..	98.2	..	0	..	98.6	..	2
20	163	+	a	....	..	0	..	99.0	..	0	..	98.8	..	0	..	98.2	P	0	..	99.2	..	0	..	98.6	..	0	..	98.2	..	1
21	172	+	a	....	..	0	..	99.2	P	0	..	99.4	..	0	..	98.2	P	0	..	99.6	..	0	..	98.8	..	0	..	99.0	..	1
22	174	+	..	....	P	+	..	99.8	..	0	..	100.0	..	0	..	98.8	..	0	..	99.0	..	0	..	99.4	..	0	..	98.8	..	2
23	178	+	a	....	..	+	a	99.2	P	+	..	99.6	P	0	..	98.6	P	0	..	98.6	..	0	..	98.8	..	0	..	98.6	..	3
24	181	+	a	....	..	0	..	99.4	..	0	..	99.0	..	0	..	99.0	..	0	..	99.6	..	+	a	99.0	P	0	..	99.8	..	2
25	182	+	v	....	..	0	..	98.7	..	0	..	98.4	P	0	..	99.0	P	+	v	99.0	P	+	a	98.8	..	0	..	98.6	..	3
26	191	+	a	....	..	+	a	99.8	P	0	..	99.0	P	0	..	98.8	P	0	..	99.4	P	0	..	98.6	P	0	..	98.6	..	2
27	198	+	v	....	..	+	v	98.4	..	0	..	99.6	P	+	v	99.0	..	0	..	99.0	P	0	..	98.8	..	0	..	99.2	..	3
28	199	+	a	....	..	+	a	99.1	..	0	..	98.6	..	0	..	100.1	P	0	..	98.6	P	0	..	98.2	..	0	..	....	P	2
29	213	+	a	....	P	+	a	99.0	P	0	..	99.4	P	0	..	98.0	P	+	a	99.6	P	+	a	99.2	P	0	..	99.0	P	4
30	218	+	a	....	..	+	..	99.0	..	0	..	99.0	..	0	..	98.0	..	0	..	99.0	..	..	..	....	..	..	..	....	..	2
31	241	+	a	....	P	0	..	98.4	P	0	..	100.0	P	+	a	98.8	P	+	a	99.8	P	+	..	98.4	P	0	..	....	P	4
32	251	+	a	....	P	+	..	98.2	P	+	..	98.6	..	+	a	98.2	..	+	..	98.6	P	+	a	98.0	..	0	..	....	..	6
33	268	+	a	....	..	0	..	98.0	P	0	..	98.8	..	0	..	99.4	P	0	..	99.0	..	0	..	98.8	..	+	a	99.2	..	2
34	326	+	a	....	..	0	..	97.9	..	0	..	99.4	..	0	..	100.2	P	0	..	98.6	..	0	..	99.4	P	0	..	98.8	..	1
35	327	+	a	....	P	0	..	97.8	P	0	..	98.2	..	0	..	98.2	P	0	..	98.6	P	0	..	99.0	P	0	..	97.6	..	1
36	331	+	a	....	..	0	..	98.2	..	0	..	98.8	P	0	..	99.4	..	0	..	99.4	..	0	..	100.0	..	0	..	99.8	..	1
37	336	+	a	....	P	0	..	97.8	P	0	..	98.8	P	0	..	99.2	P	0	..	98.8	..	0	..	99.8	P	0	..	99.4	..	1
38	344	+	a	....	..	+	..	98.4	P	0	..	99.0	P	0	..	98.8	..	0	..	98.7	..	0	..	98.2	..	0	..	98.2	..	2
39	345	+	a	....	P	+	a	98.4	P	0	..	99.2	P	0	..	99.2	P	0	..	99.0	P	0	..	98.6	P	0	..	98.8	P	2
40	357	+	a	....	..	+	a	98.2	..	0	..	99 8	P	0	..	99.0	..	0	..	99.0	..	0	..	98.2	..	0	..	98.0	..	2
41	362	+	a	....	..	0	..	97.0	..	0	..	98.0	..	0	..	97.6	..	0	..	98.2	..	0	..	98.2	..	0	..	98.4	..	1
42	366	+	a	....	..	0	..	98.6	P	0	..	98.8	..	0	..	99.0	..	0	..	99.0	P	0	..	100.6	P	0	..	98.2	..	1
43	372	+	a	....	..	+	..	97.4	P	+	a	99.0	P	+	a	98.2	..	+	a	99.8	P	+	a	99.8	..	0	..	99.6	P	6
44	376	+	..	....	..	+	..	99.0	P	0	..	99.2	..	0	..	97.3	..	0	..	99.4	P	0	..	98.2	..	0	..	98.6	..	2
45	379	+	a	....	..	+	..	98.0	P	0	..	98.2	..	0	..	97.6	..	0	..	98.8	P	0	..	99.4	..	+	a	98.0	..	3
46	382	+	a	....	..	+	a	97.2	P	+	a	98.0	P	0	..	98.0	..	0	..	96.2	..	0	..	98.0	..	0	..	....	..	3
47	385	+	a	....	..	0	..	97.7	..	+	a	98.8	P	0	..	98.4	..	0	..	98.8	..	0	..	98.2	..	0	..	98 6	..	2
48	396	+	a	....	..	0	..	98.3	P	0	..	98.4	P	0	..	98.8	..	0	..	98.7	..	0	..	98.2	P	0	..	98.0	..	1
49	402	+	a	....	..	+	..	99.0	P	+	a	99.0	..	0	..	98.2	..	0	..	98.6	P	+	a	98.4	..	0	..	98.2	..	4
50	482	+	a	....	..	+	..	99.2	..	0	..	100.0	..	0	..	99.2	..	0	..	99.4	..	0	..	98.0	..	0	..	98.2	..	2
			50				29				15				11				12				12				6			135

2. Virulent and avirulent organisms may be present in the throat at the same time and in isolating them sometimes one and sometimes the other may be obtained.

3. The carrier may lose the organism originally present and re-infestation with another organism of different virulence may take place.

Evidence against the first hypothesis is furnished by the following experiment: Five healthy persons were selected and shown to be free from diphtheria bacilli by daily throat cultures over a period of two weeks. Their throats were then inoculated with a pure culture of avirulent diphtheria bacilli and thereafter daily cultures were taken for a period of weeks, then at intervals of a few days for more than three months, and subsequently at longer intervals for about 15 months. Some of these individuals became carriers as the result of this experiment and their cultures were almost regularly positive for the first few months. Thereafter, in two of the individuals positive cultures were obtained at irregular intervals for as long as 18 months after the beginning of the experiment. From time to time the organisms were isolated in pure culture from the throats of these five persons and tested for virulence. They constantly proved avirulent and at no time did any symptoms develop in the subjects of this experiment referable to the diphtheria bacilli present in their throats.*

That the second hypothesis, the presence of virulent and avirulent bacilli in the throat of the same person, is improbable is indicated by the fact that in many of the school children who were found to harbor diphtheria bacilli, as many as six isolations were made from a single positive culture and each separate isolation tested for virulence. The results were invariably constant. The organisms were either all virulent or all avirulent, which would have been improbable if virulent and avirulent organisms had been present in the same person.

4. *To determine whether any relation exists between the presence of diphtheria bacilli and pathological throat conditions other than clinical diphtheria.*

We shall compare first the incidence of pathological throat conditions occurring in children having positive cultures with the incidence of pathological throat conditions occurring in children having negative throat cultures. This comparison is summarized in Table XII which shows in detail the results obtained at each re-examination as well as the total results obtained for all of the examinations.

TABLE XII

	Pos. cult.	Path. throat	Neg. cult.	Path. throat
2d exam.....	29	17—58.62%	21	12—57.14%
3d exam.....	15	7—46.66%	35	16—45.71%
4th exam.....	11	6—54.54%	39	19—48.72%
5th exam.....	12	8—66.67%	38	15—39.47%
6th exam.....	12	5—41.67%	37	8—21.62%
7th exam.....	6	2—33.33%	42	7—16.66%
	85	45—52.94%	212	77—36.32%

* A detailed account of this work is to be reported in another paper.

The table shows that for each examination a higher percentage of pathological throat conditions was found in children with positive cultures than in children with negative cultures. The total result for all six examinations shows that 52.94 per cent of the children with positive cultures had pathological throat conditions as compared with 36.32 per cent pathological throat conditions among the children with negative cultures.

If now we compare the incidence of positive cultures in children with pathological throat conditions with the incidence of positive cultures in children having normal throats we get similar results (Table XIII).

TABLE XIII

	Path. throat	Pos. cult.	Norm. throat	Pos. cult.
2d exam.....	29	17—58.62%	21	12—57.14%
3d exam.....	23	7—30.43%	27	8—29.63%
4th exam.....	25	6—24.00%	25	5—20.00%
5th exam.....	23	8—34.78%	27	4—14.81%
6th exam.....	13	5—38.46%	36	7—19.44%
7th exam.....	9	2—22.22%	39	4—10.25%
	122	45—36.88%	175	40—22.85%

At each examination children with pathological throat conditions yielded a higher percentage of positive cultures than did children with normal throats. The totals for the six re-examinations show 36.88 per cent positive cultures occurring in children with pathological throats as compared with 22.85 per cent cultures in children with normal throats.

We are unable to say which is cause and which is effect, although the question seems of some importance. May the presence of diphtheria bacilli in the throat give rise to pathological conditions which do not attain the proportions of those occurring in clinical diphtheria or does the presence of pathological throat conditions favor the lodgment and growth of diphtheria bacilli in the throat? Experience rather points to the latter view since it has been shown that in many instances diphtheria bacilli disappear from the throat after the removal of diseased tonsils. That they persist in some cases after tonsillectomy is to be expected, as their habitat may be lymphadenoid tissue in the nasopharynx other than the tonsils, the nasal passages or the paranasal sinuses.

To gain further light on these questions we have attempted to analyze the relation of positive cultures and pathological throat conditions to elevations of temperature.

The results for the six re-examinations are shown in Table XIV.

The results in Table XIV are not so uniform as those shown in the two preceding tables. At four out of six examinations temperature elevations occurred in a higher percentage of

children with positive cultures than in those with negative cultures and the summary for the six examinations shows temperature elevation in 37.77 per cent of the children with positive cultures as compared with 32.85 per cent of children with negative cultures.

TABLE XIV

	Positive cultures		Negative cultures		Path. throats		Normal throats	
	Total	With temp. over 99° F.	Total	With temp. over 99° F.	Total	With temp. over 99° F.	Total	With temp. over 99° F.
2d....	29	8—27.58%	21	4—19.05%	29	7—24.13%	21	5—23.81%
3d....	15	10—66.67%	34	13—38.23%	23	10—43.47%	26	13—50.00%
4th...	11	2—18.18%	39	11—28.20%	25	8—32.00%	25	5—20.00%
5th...	12	7—58.33%	38	16—42.10%	23	9—39.13%	27	14—51.85%
6th...	12	4—33.33%	37	12—32.43%	13	4—30.77%	36	12—3 .33%
7th...	6	1—16.67%	38	12—31.57%	7	2—28.57%	37	11—29.73%
	85	32—37.77%	207	68—32.85%	120	40—33.33%	172	60—34.88%

With regard to throat conditions the percentage of temperature elevations was practically the same in the group with pathological throats and in those with normal throats, 33.33 per cent and 34.88 per cent respectively.

An attempt has been made to analyze the combined influence of positive cultures and pathological throat conditions on the temperature reaction. The results are seen in Table XV.

TABLE XV

	Pos. cult. and path. throat		Pos. cult. and normal throat		Neg. cult. and path. throat		Neg. cult. and normal throat	
	Total	With temp. over 99° F.	Total	With temp. over 99° F.	Total	With temp. over 99° F.	Total	With temp. over 99° F.
2d....	17	4	12	4	12	3	9	1
3d....	7	4	8	6	16	6	18	7
4th...	6	2	5	0	19	6	20	5
5th...	8	3	4	4	15	6	23	10
6th...	5	1	7	3	8	3	29	9
7th...	2	1	4	0	5	1	33	11
	45	15—33.33%	40	17—42.50%	75	25—33.33%	132	43—32.57%

It appears that in the series under consideration temperature elevations over 99° F. occurred with about the same frequency in the following three groups: Positive culture and pathological throat, 33.33 per cent; negative culture and pathological throat, 33.33 per cent; and negative culture and normal throat, 32.57 per cent. Temperature elevations occurred somewhat more frequently in the group with positive cultures and normal throats, 42.50 per cent.

5. *To determine by history and observation whether:*

(a) *Any of the carriers investigated have at any previous time had clinical diphtheria,*

(b) *Any of them develop clinical diphtheria during the period they are under observation,*

(c) *Any of them has ever been exposed to a case of clinical diphtheria,*

(d) *Any one in contact with the carriers investigated develops clinical diphtheria.*

In the present state of our knowledge the most vital question in regard to diphtheria bacillus carriers seems to be their relation to the community; that is, how serious a menace they constitute.

Having as a result of the present investigation 160 carriers * under observation we determined to see whether we could confirm the observations reported in our previous communication on this subject. The results are shown in Table XVI.

Summary of answers to the five questions in Table XVI:

1. Had you had diphtheria previous to the time the throat culture was taken?

149 negative replies.
11 affirmative replies.

1 No. 163 ..... Diphtheria when a baby
1 No. 53 ..... Diphtheria when a small child
1 No. 276 ..... Diphtheria 3 years ago
1 No. 65 ..... Diphtheria 5 years ago
3 Nos. 75, 247, 500 ..... Diphtheria 6 years ago
4 Nos. 80, 396, 416, 471.. Diphtheria 8 years ago

2. Have you had diphtheria since the culture was taken?

160 negative replies.

3. Had you been exposed to a case of diphtheria before the culture was taken?

146 negative replies.
14 affirmative replies.

2 Nos. 599, 787 ..... Exposed 1 year ago
1 No. 433 ..... Exposed 2 years ago
2 Nos. 31, 693 ..... Exposed 3 years ago
3 Nos. 37, 112, 651 ..... Exposed 4 years ago
2 Nos. 454, 486 ..... Exposed 5 years ago
2 Nos. 126, 522 ..... Exposed 6 years ago
1 No. 567 ..... Exposed 8 years ago
1 No. 102 ..... Exposed 12 years ago

4. Has any one with whom you have been associated developed diphtheria since the culture was taken?

160 negative replies.

5. Have you had any throat trouble during past year, if so, of what nature?

143 negative replies.
17 affirmative replies.

9 Nos. 61, 344, 345, 362, 368, 460, 530, 749, 756. Sore throat treated at home without physician
2 Nos. 47, 613 ..... Sore throat treated at home by physician
5 Nos. 164, 326, 383, 500, 687 ..... Sore throat. No note as to physician
1 No. 483 ..... Sore throat. Tonsillectomy 1912

* The number of individuals with positive cultures at the first examination of the 800 children was 85, as mentioned in Part I, and from these were selected the 50 carriers for the more intensive study reported in Part II. The second examination of the 800 children revealed 69 carriers, only 10 of whom were positive at the earlier test, giving us 144 individuals positive one time or the other. As the result of additional cultures taken on some of these same 800 children but not included in this report, 16 other carriers were discovered and since they were available, the entire 160 were used for the study of their relation to the community.

These results require little in the way of comment. We realize that one cannot rely implicitly on the accuracy of replies made by school children to such a set of questions as the above, but as much care as possible was exercised in trying to obtain accurate histories and not only were the children questioned but they were visited in their homes by the school nurse, Mrs. H. E. Knorr, who carried out this part of the investigation and questioned the parents and guardians of the children most carefully. Moreover, the children themselves were under observation for a considerable length of time in the school and we could learn of no case of diphtheria developing among them or any of their associates.

THE NATURE OF THE DIPHTHERIA BACILLI PRESENT IN THE POSITIVE CULTURES

At this point a few words may be appropriate about the "diphtheria bacilli" present in the "positive cultures." Unless specific statements are made concerning the methods employed for their recognition, questions are apt to arise as to the identity of the organisms present in the throats of these carriers and assumed by us to be Klebs-Loeffler bacilli. Among the questions to be anticipated might be mentioned the following:

Were we dealing with "pseudo-diphtheria bacilli"? *B. xerosis* or *B. hofmanni?* Barred, banded or solid-staining forms? Diphtheroid organisms?

How would they be classified on the Wesbrook-Wilson-McDaniel scale? As A or C_2? As B_2 or G?

As the result of our experience in 1911, we felt prepared to recognize *B. diphtheriæ* as it appears in mixed culture from the throats of carriers. In the present work, accordingly, our original diagnosis was based solely upon the morphology, arrangement and staining characteristics of the organisms seen in films from 18- to 24-hour cultures on Loeffler's blood serum and stained by the Neisser method. To check this original diagnosis an attempt was made to isolate the diphtheria organisms present in the positive cultures. This was carried out and the pure cultures subjected to further examination in 163 instances * as follows:

1. Staining by Neisser, Loeffler's methylene blue and Gram methods.
2. Observation of cultural characteristics.
3. Tests for virulence.

The results of these tests on pure cultures may be summarized briefly:

1. *Staining and Morphology.*—After growth on Loeffler's serum for 18 to 24 hours the organisms were for the most part long and slender, showing polar granules prevailingly terminal in location and a marked tendency to typical group arrangement in angles and parallels. All would be classified as A, C, or D on the Wesbrook scale, with the long, slender form C greatly preponderating, while types A and D were rarely encountered. With the Neisser stain most satisfactory results were obtained when the methylene blue and Bismarck brown were each allowed to act for from three to five minutes instead of as many seconds in the way usually recommended. With the Gram stain the polar granules retained the stain, the bodies being much less resistant to decolorization by alcohol.

2. *Cultural Characteristics.*—On Loeffler's blood serum the growth was relatively abundant and the colonies round, discrete, opaque, rather putty-like in color and consistence and never causing liquefaction of the medium.

On plain agar the growth was definite but feebler, scantier and the individual colonies tiny.

In litmus milk there was no coagulation but a definite change of color was produced as compared with the slightly alkaline control tubes—the resultant color being a lilac shade indicating a slight change of reaction from alkaline to neutral.

In bouillon a slight surface film was frequently seen, its presence apparently depending to a considerable extent on the method used in inoculating the tube. Slight turbidity might be observed early, but for the most part the medium was clear and a deposit of tiny granules could be seen on the sides and bottom of the tube capable of producing slight but definite turbidity when the tube was shaken.

The tests for the action on sugars were performed with sugar-free broth to which the sugar was added prior to the final sterilization. No test was considered satisfactory unless a good growth was obtained in the broth. The organisms all produced acid but no gas with dextrose, while neither acid nor gas was formed from saccharose.

3. *Virulence Tests.*—A positive result was reported when the animal died within 4 days after injection and showed characteristic lesions at autopsy, while the protected, control, animal survived. In most instances the virulent organisms killed within two days. All surviving animals were kept under observation for weeks after the date of injection. The results of these tests are reported elsewhere in this paper, but it may be mentioned here that many of the cultures were tested on guinea-pigs more than once, some of them many times, and the original result confirmed in each instance.

Diphtheria-Like Organisms.—From the throat cultures regarded as negative but containing any organisms resembling even remotely the diphtheria bacillus, isolations were made in like manner. When in pure culture many of them could be ruled out at once on a basis of morphology and staining characteristics or the appearance of the growth on blood serum. Of the remainder, practically all were members of the "diphtheria group" of organisms, resembling rather closely the diphtheria bacillus in their growth on Loeffler's medium, but easily differentiated from it by their size, shape and staining characteristics, despite their rather typical arrangement. This was

* *B. diphtheriæ* was isolated from all except a very few of the positive cultures obtained and referred to in Parts I and II of this paper, but unfortunately many of the strains were lost before their examination was completed. This occurred as the result of transference to a lot of Loeffler's serum which had been insufficiently sterilized; when this was discovered many of our cultures were hopelessly overgrown with *B. subtilis*. Thus, although practically all had been previously examined as to staining and cultural characteristics, only 163 stains were available for the complete study, including the test for virulence.

TABLE XVI

Culture number	Diphtheria previous to culture	Diphtheria subsequent to culture	Exposure to diphtheria previous to culture	Diphtheria in associates subsequent to culture	Any throat trouble in past year	Remarks
4	No.	No.	No.	No.	No.	
15	"	"	"	"	"	
20	"	"	"	"	"	
24	"	"	"	"	"	
25	"	"	"	"	"	
31	"	"	Yes.	"	"	Brother died of diphtheria 3 years ago.
35	"	"	No.	"	"	
37	"	"	Yes.	"	"	Brother had diphtheria 4 years ago. Recovered. House fumigated.
47	"	"	No.	"	Yes.	Severe sore throat during past winter. Treated by physician. Diagnosis: tonsillitis.
48	"	"	"	"	No.	
50	"	"	"	"	"	
53	Yes.	"	"	"	"	Has been told that he had diphtheria when a small child.
55	No.	"	"	"	"	
61	"	"	"	"	Yes.	Severe sore throat during past winter. Treated at home without physician. Recovered after 3 days.
65	Yes.	"	"	"	No.	Diphtheria 5 years ago.
67	No.	"	"	"	"	
69	"	"	"	"	"	
70	"	"	"	"	"	
72	"	"	"	"	"	
75	Yes.	"	"	"	"	Diphtheria 6 years ago. Tonsils removed 3 years ago.
77	No.	"	"	"	"	
80	Yes.	"	"	"	"	Had diphtheria 8 years ago. Antitoxin used. House fumigated.
87	No.	"	"	"	"	Had repeated attacks of sore throat prior to 1911 when tonsils were removed.
102	"	"	Yes.	"	"	Sister had diphtheria 12 years ago. Pupil then 1 year old.
112	"	"	"	"	"	Sister had diphtheria 4½ years ago.
122	"	"	No.	"	"	
126	"	"	Yes.	"	"	Exposed 6 years ago. Cousin visited pupil's home for one day. Complained of sore throat. Diagnosed as diphtheria a few days later. Pupil then 7 mos. old.
130	"	"	No.	"	"	
131	"	"	"	"	"	
133	"	"	"	"	"	
134	"	"	"	"	"	Sister had diphtheria 15 years ago, 8 years before birth of patient.
147	"	"	"	"	"	
148	"	"	"	"	"	Sister had diphtheria before birth of pupil.
149	"	"	"	"	"	
150	"	"	"	"	"	
153	"	"	"	"	"	
159	"	"	"	"	"	Sister had diphtheria 15 years ago, 8 years before birth of pupil.
163	Yes.	"	"	"	"	Has been told that she had diphtheria when a baby.
164	No.	"	"	"	Yes.	Had severe tonsillitis during past winter.
172	"	"	"	"	No.	
173	"	"	"	"	"	
174	"	"	"	"	"	
178	No.	No.	No.	No.	No.	
179	"	"	"	"	"	
181	"	"	"	"	"	Had severe sore throat 8 years ago. Treated by physician. Reported as having been very ill.
182	"	"	"	"	"	
191	"	"	"	"	"	
198	"	"	"	"	"	
199	"	"	"	"	"	
204	"	"	"	"	"	
207	"	"	"	"	"	
209	"	"	"	"	"	
213	"	"	"	"	"	
221	"	"	"	"	"	
231	"	"	"	"	"	
232	"	"	"	"	"	
234	"	"	"	"	"	
241	"	"	"	"	"	Sister had diphtheria 10 years ago, before birth of pupil.
242	"	"	"	"	"	
247	Yes.	"	"	"	"	Had diphtheria 6 years ago.
251	No.	"	"	"	"	Brother had diphtheria 5 years ago, before birth of pupil.
254	"	"	"	"	"	
258	"	"	"	"	"	
268	"	"	"	"	"	
276	Yes.	"	"	"	"	Had diphtheria 3 years ago. Flat fumigated. Antitoxin used.
278	No.	"	"	"	"	
305	"	"	"	"	"	
311	"	"	"	"	"	
321	"	"	"	"	"	
326	"	"	"	"	Yes.	Had severe sore throat several months ago. Throat culture at the time negative for *B. diphtheriæ*.
327	"	"	"	"	No.	
331	"	"	"	"	"	
332	"	"	"	"	"	
336	"	"	"	"	"	
344	"	"	"	"	Yes.	Had severe sore throat during past winter. Treated at home without physician. Recovery in less than a week.
345	"	"	"	"	"	Had severe sore throat during past winter. Treated at home without physician. Recovered in less than a week.
354	"	"	"	"	No.	
355	"	"	"	"	"	
357	"	"	"	"	"	
362	"	"	"	"	Yes.	Had severe sore throat during past winter. Treated at home without physician. Lasted about one week.
363	"	"	"	"	No.	
366	"	"	"	"	"	
368	"	"	"	"	Yes.	Had sore throat during past winter. Treated at home without physician.

TABLE XVI—*Continued*

Culture number	Diphtheria previous to culture	Diphtheria subsequent to culture	Exposure to diphtheria previous to culture	Diphtheria in associates subsequent to culture	Any throat trouble in past year	Remarks
372	No.	No.	No.	No.	No.	Sister had diphtheria 15 years ago, before birth of pupil
376	"	"	"	"	"	
379	"	"	"	"	"	
382	"	"	"	"	"	
383	"	"	"	"	Yes.	Had sore throat during past winter.
385	"	"	"	"	No.	
386	"	"	"	"	"	
396	Yes.	"	"	"	"	Had diphtheria 8 years ago. Antitoxin used. House fumigated.
402	No.	"	"	"	"	
404	"	"	"	"	"	
409	"	"	"	"	"	
411	"	"	"	"	"	
413	"	"	"	"	"	
414	"	"	"	"	"	
416	Yes.	"	"	"	"	Had diphtheria 8 years ago. Antitoxin used. House fumigated.
419	No.	"	"	"	"	
423	"	"	"	"	"	
433	"	"	Yes.	"	"	Playmate had diphtheria 2 years ago.
434	"	"	No.	"	"	
446	"	"	"	"	"	
449	"	"	"	"	"	
450	"	"	"	"	"	
454	"	"	Yes.	"	"	Brother had diphtheria 5 years ago. Antitoxin used. House fumigated.
460	"	"	No.	"	Yes.	Had sore throat during past winter. Treated at home without physician.
463	"	"	"	"	No.	
467	"	"	"	"	"	
469	"	"	"	"	"	
471	Yes.	"	"	"	"	Had diphtheria 8 years ago. Antitoxin used. House fumigated.
481	No.	"	"	"	"	
482	"	"	"	"	"	
483	"	"	"	"	Yes.	Repeated mild attacks of sore throat. Tonsils removed April, 1912.
486	"	"	Yes.	"	No.	Brother had diphtheria 5 years ago.
490	"	"	No.	"	"	
493	"	"	"	"	"	
496	"	"	"	"	"	
500	Yes.	"	"	"	Yes.	Had diphtheria 6 years ago. Had severe sore throat during past winter. Enlarged tonsils.
522	No.	"	Yes.	"	No.	Brother had diphtheria 6 years ago. Antitoxin used. House fumigated.
530	"	"	No.	"	Yes.	Had sore throat during past winter. Not severe. Treated at home without physician. Enlarged tonsils.
531	"	"	"	"	No.	
534	"	"	"	"	"	
535	No.	No.	No.	No.	No.	
556	"	"	"	"	"	
567	"	"	Yes.	"	"	Brother and sister had diphtheria 6 years ago.
576	"	"	No.	"	"	
578	"	"	"	"	"	
582	"	"	"	"	"	
591	"	"	"	"	"	
592	"	"	"	"	"	
599	"	"	Yes.	"	"	Case of diphtheria in same house one year ago. House fumigated afterwards.
603	"	"	No.	"	"	
613	"	"	"	"	Yes.	Had severe sore throat July, 1912. Treated by physician. Not confined to bed.
628	"	"	"	"	No.	
650	"	"	"	"	"	
651	"	"	Yes.	"	"	Brother had diphtheria 4 years ago. Pupil sent to live elsewhere after diagnosis was made; returned home after house was fumigated.
670	"	"	No.	"	"	
672	"	"	"	"	"	
675	"	"	"	"	"	
678	"	"	"	"	"	
679	"	"	"	"	"	
684	"	"	"	"	"	
687	"	"	"	"	Yes.	Had several mild attacks of sore throat during past winter. Enlarged tonsils.
691	"	"	"	"	No.	
693	"	"	Yes.	"	"	Brother had diphtheria 3 years ago. Antitoxin used and flat fumigated.
702	"	"	No.	"	"	
705	"	"	"	"	"	
717	"	"	"	"	"	
718	"	"	"	"	"	
730	"	"	"	"	"	
732	"	"	"	"	"	
733	"	"	"	"	"	
736	"	"	"	"	"	
749	"	"	"	"	Yes.	Had sore throat during past winter. Treated at home without physician.
756	"	"	"	"	"	Had severe sore throat during past winter. Treated at home without physician.
760	"	"	"	"	No.	
783	"	"	"	"	"	
787	"	"	Yes.	"	"	Playmate living in same house had diphtheria one year ago.
796	"	"	No.	"	"	

confirmed when tested on litmus milk and sugars, as these organisms reacted quite differently from *B. diphtheriæ*, producing no acid with either dextrose or saccharose but definite increase in alkalinity with litmus milk. These organisms could be classified, therefore, as *B. hofmanni*. The xerosis bacillus which produces acid with both dextrose and saccharose was very rarely encountered, probably because we were dealing with cultures from the throat rather than the nose.

All of these organisms of the "diphtheria group" isolated from throat cultures regarded by us as negative were also tested for virulence, the number of strains thus tested being quite as large as that of true diphtheria bacilli. No virulent strain was encountered and they seemed to be uniformly without pathogenicity.

As a result of this study of the organisms isolated from the throat cultures we concluded that:

1. The original diagnosis of cultures positive or negative for *B. diphtheriæ* was confirmed.

2. The "avirulent diphtheria bacilli" of which we speak are indistinguishable from true, virulent *B. diphtheriæ* except by the animal test of toxin production.

3. The other members of the diphtheria group of organisms encountered in cultures from the throat need cause very little difficulty in recognition and are of no pathogenic importance.

Summary, Part II

It should be borne in mind that whereas Part I of this paper deals with the results of examination of 800 school children, some of whom were found to be diphtheria bacillus carriers, Part II concerns the further study of 50 of these same children, all of whom were shown to be carriers at the time the investigation was begun. Consequently, since certain of the conditions were so different in the two groups studied and 50 of the children appear in both groups, not all of the results reported in the first portion can be directly compared with those in the second. Thus, in Part I the percentage incidence of bacillus carriers is emphasized, while in Part II which is concerned only with carriers, it is the persistence of the bacilli—the duration of the carrier state—which receives attention. In the following summary of the findings in Part II, therefore, only such portions of the results recorded in Part I as have a definite bearing on the subject in hand, will be included for comparison; these are placed in brackets.

1. *How long may diphtheria bacilli persist in the throats of persons having positive cultures but not suffering from clinical diphtheria?*

Fifty children who had positive cultures at the time of the first examination were re-examined at intervals of two weeks over a period of three months. The total number of cultures made on the six re-examinations was 297, of these 85, or 28.62 per cent., were positive. At the time of the last examination diphtheria bacilli were found in only six of the 50 children.

2. *What is the virulence of the diphtheria bacilli present in the throats of carriers?*

Cultures from 47 of the children in the above series were tested for virulence and six found virulent, 12.76 per cent.

Of the 135 positive cultures obtained from the 50 children selected for repeated examination, virulence tests were performed on 110; 12, or 10.90 per cent, were found virulent.

(In Part I we reported (1) that of the 85 positive cultures encountered in the first examination of the 800 children, 64 were tested by guinea-pig inoculation and eight, or 12.50 per cent, found virulent; (2) that on the second examination 41 of the 69 positive cultures were tested and 3, or 7.31 per cent, found virulent; (3) that in all, cultures from 99 different children were tested and 11, or 11.11 per cent, were virulent.)

3. *Do diphtheria bacilli growing in the throats of carriers undergo a change in virulence?*

In the case of three of the carriers in this series sometimes virulent organisms and sometimes avirulent organisms were found. This fact does not constitute proof that avirulent organisms acquired virulence or that virulent organisms became avirulent.

4. *Does any relation exist between the presence of diphtheria bacilli and pathological throat conditions other than clinical diphtheria?*

Pathological throat conditions were found more frequently in children who had positive cultures than in those with negative cultures, 52.94 per cent in the former and 36.32 per cent in the latter.

(In the first examination of the 800 children reported in Part I, pathological throat conditions were found in 29.41 per cent of those with positive cultures and in 26.01 per cent of those with negative cultures. At the second examination, the difference was more striking, 21.73 per cent and 12.58 per cent.)

A higher percentage of positive cultures was found in children with pathological throats than in those with normal throats, 36.88 per cent in the former and 22.85 per cent in the latter.

(The same holds true for Part I; at the first examination 11.84 per cent of positive cultures were found in the children with pathological throats and 10.18 per cent in those with normal throats. At the second examination the difference was more pronounced, 14.01 per cent and 7.93 per cent.)

Temperature elevations occurred slightly more frequently among children giving positive cultures than among those giving negative cultures.

(The exact reverse of this was found in the study of the 800 children reported in Part I.)

Temperature elevations occurred with about equal frequency among children having pathological throats and among those with normal throats.

(This is in agreement with the findings with the other group of children.)

Studying the combined influence of culture and throat condition on the temperatures, we found that the highest percentage of temperature elevations occurred in the group with positive cultures and normal throats.

(To quote from Part I, "It was found that the incidence of temperature elevations was about equal in the following three groups:

(a) Positive culture and pathological throat.

(b) Negative culture and pathological throat.

(c) Negative culture and normal throat.

The incidence of temperature elevations was considerably less in the group with positive cultures and normal throats."

We do not pretend to reconcile this statement with the findings in Part II indicated above, nor is the matter simplified by a further quotation from Part I as follows: "If we regard as carriers those children who gave at either examination a positive culture, we find the highest incidence of temperature elevations occurring in any group was among carriers who had pathological throat conditions.")

Our general impression upon this point is that the mere presence of diphtheria bacilli in the throats of carriers is not responsible for any objective pathological condition whatever, and does not cause an elevation of temperature. On the other hand, persons with pathological throat conditions other than clinical diphtheria, particularly those with diseased tonsils, seem to furnish a somewhat more favorable field for the lodgment and growth of the diphtheria bacillus than that afforded by persons with normal throats.

5. *What is the previous and subsequent history and the relation to the community with reference to clinical diphtheria of persons having positive cultures?*

An investigation of 160 diphtheria bacillus carriers to determine these points yielded the following results:

(a) Only 11 of the 160 carriers gave a history of having had diphtheria, but none more recently than three years previous to the time throat cultures were taken.

(b) None of the 160 carriers subsequently developed diphtheria during the period that they were under observation.

(c) Fourteen of the 160 carriers gave a history of exposure to diphtheria at a period varying from 1 to 12 years previous to the time cultures were made.

(d) A painstaking investigation revealed no case of diphtheria developing among any of the associates of the 160 carriers.

6. *What is the nature of the diphtheria bacilli present in the positive cultures?*

This has been covered in the section devoted to this subject, but our conclusions may be repeated here. The diphtheria bacilli found in the throats of these carriers were in all respects typical Klebs-Loeffler organisms. The non-virulent diphtheria bacilli apparently differ from the virulent bacilli only in their ability to produce toxin. Since the other members of the diphtheria group encountered in the throat are readily distinguished from *B. diphtheriæ*, they need cause very little difficulty in diagnosis. They are of no pathogenic importance.

CONCLUSIONS

We have preferred not to draw a large number of conclusions from these investigations, thinking it wiser merely to state the results obtained. With regard to a few points, however, owing to their importance, we wish to express our conviction.

First: The diphtheria bacilli present in a majority of healthy carriers * are avirulent.

Second: Avirulent bacilli cannot produce diphtheria.

Third: We have no proof that avirulent diphtheria bacilli can acquire virulence.

For the above reasons we conclude that the carriers of avirulent diphtheria bacilli do not constitute a menace to any one in particular or the community as a whole and that any interference with their liberties on the grounds of their being carriers is unwarranted and not justifiable.

This stand, of course, immediately raises the question as to what constitutes a valid test of virulence. We believe that the standard guinea-pig test may be taken as a safe index of the virulence or non-virulence of diphtheria bacilli for human beings. We have a certain amount of evidence in support of this belief to be presented in a subsequent paper. It may be justifiable, and under certain conditions advisable, to isolate carriers until the virulence of the organism present can be determined, but if the culture proves avirulent for the guinea-pig, further detention of the carrier does not seem justifiable.

We realize fully the time and expense entailed in applying the guinea-pig test, but think this does not equal the inconvenience to the individual and economic loss incurred by needless isolation of a carrier of avirulent bacilli.

There is urgent need of a simpler, quicker and less expensive virulence test.

Fourth: The carrier of virulent diphtheria bacilli occupies quite a different position from that of the carrier of avirulent bacilli. While we think that the danger from the former has perhaps been overestimated we recognize the fact that diphtheria bacilli derived from him may give rise to the disease in susceptible persons. In this connection we have pointed out in a previous communication the need of a satisfactory and efficient means of ridding carriers of virulent diphtheria bacilli.

* The term "healthy" carrier is used in distinction to "convalescent" or "contact" carrier.

ERRATUM

Attention is called to a typographical error on page 364 of the October BULLETIN, in the article entitled "The Coagulation Time of Citrated Plasma on Recalcination," by H. C. Gram. The fourth paragraph, second column, should read as follows:

"About 4.5 c. cm. of blood are taken with a curved needle into a centrifuge tube divided into tenths of a c. cm. and containing .5 c. cm. of 10 per cent sodium citrate solution. After standing for about an hour the corpuscles will have sedimented—excepting in cases of polycythæmia—so as to allow one to draw off .1 c. cm. of plasma for each of the four miniature test-tubes which have previously been inserted into the holes in the cork of the Dewar flask."

THE TREATMENT OF NEUROSYPHILIS BY THE INTRASPINAL ROUTE

WITH THE REPORT OF A CLINICAL STUDY OF A SERIES OF CASES TREATED FROM THE POINT OF VIEW OF INCREASED PERMEABILITY OF THE MENINGES

By Albert Keidel and Joseph Earle Moore

(From the Syphilis Department of the Medical Clinic of The Johns Hopkins Hospital)

Since the introduction by Swift and Ellis[1] of a practical method for the intraspinal treatment of neurosyphilis, testimony has been forthcoming from many sources in favor of its efficacy in cases which stubbornly refuse to yield to ordinary methods of treatment. That this indorsement is not unanimous, however, is seen in the objections raised by some authors, notably Sachs and Dercum.

Sachs[2] objects to intraspinal medication on the grounds that it is of no more clinical or serological value than the routine administration of arsphenamine intravenously combined with mercury in some form. Dercum,[3] in a recent review of the subject, condemns intraspinal therapy as unscientific and claims that any benefit derived from it is wholly due to the incidental spinal drainage, from which by itself he has obtained brilliant results in the treatment of neurosyphilis.

In the main these objections have been outweighed by the work of others, but until the mechanism by which this form of treatment becomes effective is understood, uncertainty will undoubtedly continue to render the choice of a method of treatment difficult.

In 1915 Swift[4] outlined the various methods available for the intraspinal treatment of syphilis and summarized the theories and the known facts regarding the mode of action of arsphenaminized serum. His conclusions are worth reviewing: (1) such serum is spirochæticidal[5]; (2) it may contain syphilitic antibodies; (3) the normal human serum may contain substances which when brought into contact with the syphilitic exudate cause it to resolve; (4) the acute irritation produced by the serum may exert a beneficial effect on the chronic inflammatory process; and (5) the local irritation may increase the permeability of the meninges. Of these conclusions the first and third are based on experiment, while the remaining ones are inferences which, while not lacking in some experimental support, have nevertheless not as yet been proved. The fifth conclusion, that of the hypothetical increase in the permeability of the meninges, has seemed to us to be susceptible of clinical investigation by observing the extent to which this factor enters into the beneficial results of intraspinal medication. Our paper deals with this phase of of the subject.

Permeability of the meninges, or more strictly speaking, of the choroid plexuses and the meninges, in the normal individual appears to be limited almost exclusively to the production and elimination of cerebrospinal fluid. Under normal conditions substances in the blood stream, including bacteria, immune bodies, and most drugs are excluded from the cerebrospinal fluid circulation. In this sense the choroid-plexus-meningeal complex constitutes a valuable defense mechanism for the central nervous system, as illustrated for example in chronic mercurial poisoning[6,7] and septicemias.[8]

Under pathological conditions involving these structures (choroid plexus and meninges) however, their impermeability appears to be affected, and bacteria and blood elements pass into the central nervous system.[9,10] Contrary to what might be expected under this condition other substances in the blood-stream, notably drugs and possibly immune bodies, continue to be largely excluded, although there appear to be exceptions to this, as will be explained later. At any rate it may be definitely stated that failure of routine antisyphilitic treatment in neurosyphilis depends upon this difficulty for mercury and arsphenamine to pass the barrier set up by the choroid-plexus-meningeal complex in sufficient amounts to make the concentration spirochæticidal. It is assumed, however, that the pathological process has modified the defense mechanism sufficiently to permit variable quantities to pass over which may be greater than under normal conditions, and that exceptionally the amount passed might be great enough to reach the desired concentration.

Various observers, among them Benedict,[11] Sicard and Bloch,[12] and Kopke[13] have invariably succeeded in demonstrat-

[1] Swift, H. F., and Ellis, A. W. M.: New York Med. Jour., 1912, XCVI, 53.

[2] Sachs, B.: Arch. Neurol. and Psychiat., 1919 (March), I, 277.

[3] Dercum, F. X.: Arch. Neurol. and Psychiat., 1920 (March), III, 230.

[4] Swift, H. F.: J. A. M. A., 1915 (July 17), LXV, 209.

[5] Swift, H. F., and Ellis, A. W. M.: Journal Exp. Med., 1913, XVIII, 435; and Swift, H. F.: Jour. Exp. Med., 1916, XXIV, 373.

[6] Rotky: Ztschr. f. Klin. Med., 1912, LXXV, 494.

[7] Sicard, A.: Thèse de Paris, 1899.

[8] This refers to the low incidence of meningitis in septicemias generally.

[9] Mattauschek and Pilcz (Ztschr. f. d. ges. Neur. u. Psych., 1910-11, IV, Orig., 697; 1913, XV, 608) have shown in a survey of over 4000 syphilitics, followed over a long period of time, that about 25 per cent of the untreated or badly treated cases will develop clinical neurosyphilis.

[10] Many workers have demonstrated by laboratory tests abnormalities of the cerebrospinal fluid in from 25 to 35 per cent of untreated cases of secondary syphilis (period of generalization).

[11] Benedict (cited by Sachs): Am. J. M. Sc., 1914, CXLVIII, 693.

[12] Kopke and Sicard and Bloch (cited by Mestrezat, W.): Paris, 1912, Footnote 3, p. 93.

ing appreciable quantities of arsenic in the fluid after intravenous administration of arsphenamine in neurosyphilis. Hall and his associates[13] found arsenic after intravenous administration in only 25 to 35 per cent of the cases; Reiger and Solomon[14] in about the same percentage; Mehrtens and McArthur[15] in 43 per cent of the cases. In all instances the amount is small.

In this connection the work of Flexner and Amoss with poliomyelitis is of interest. They showed[16] that in human cases infected with poliomyelitis, no neutralizing substances (immune bodies) could be demonstrated in the spinal fluid, either early or late in the disease; but that in monkeys immune bodies could be made to appear in the fluid after intravenous injections of immune serum, by first setting up an aseptic meningitis[17] with the intraspinal injection of sterile horse serum. The defense mechanism of the choroid-plexus-meningeal complex was further demonstrated[18] by the following means: a simple intravenous injection of 50 c. c. of a 5 per cent suspension of active spinal cord and medulla (poliomyelitis virus) was unsuccessful in reproducing the disease. If aseptic fluids, such as normal monkey or horse serum, isotonic salt solution, and Ringer's or Locke's solution, or even spinal fluid from another monkey, were first injected intraspinally, an intravenous injection of equal or smaller amounts of virus did promote infection. This seemed to demonstrate, at least for monkeys, an exceedingly delicate defense mechanism, which even very slight irritation was capable of altering in such a way that the passage of virus or immune bodies from the blood to the spinal fluid and tissues of the central nervous system was permitted.

[13] Hall, G. W., Callender, R. J., and Holmblad, E. C.: Arch. Neurol. and Psychiat., 1920, III, 631.

[14] Reiger, J. B., and Solomon, H. C.: J. A. M. A., 1918 (July 6), LXXI, 15.

[15] Mehrtens, H. G., and MacArthur, C. G.: Arch. Neurol. and Psychiat., 1919, II, 369.

[16] Flexner, S., and Amoss, H. L.: Jour. Exp. Med., 1917, XXV, 499.

[17] The existence of an aseptic meningitis after intraspinal injections of sera, originally assumed to exist because of the meningeal symptoms of the reaction, has been proved by Weed, Wegeforth, Ayer, and Felton (see note 26) and by Hall, Callender and Holmblad.

The former found that in cats the intraspinal injection of normal cat serum provoked a cellular reaction which reached its maximum in about 6 hours, after which a sharp decrease occurred in the number of cells for about 48 hours, with a slow return to normal in 120 hours. The extent to which this reaction can reach is shown by Hall and his associates, working with human subjects. They administered autologous serum intraspinally to 18 cases, upon whom they performed repeated spinal punctures at intervals of from one hour to 113 hours after treatment. Two of the cases reacted with a cell count of over 4000, in 11 of the 18 the count rose to over 1000, and in the others nearly as high. They found the time relations essentially as given by Weed, except that the reaction was somewhat more sustained, and the counts had not subsided to normal within 113 hours.

[18] Flexner, S., and Amoss, H. L., Jour. Exp. Med., 1917, XXV, 525.

THE APPLICABILITY OF MENINGEAL PERMEABILITY TO NEUROSYPHILIS. CLINICAL METHOD OF INVESTIGATION AND RESULTS

If such a mechanism could be demonstrated for poliomyelitis it seemed reasonable to assume that it might also be made to apply to the treatment of neurosyphilis. Perhaps the permeability of the meningeal-choroid-plexus complex might be sufficiently altered by irritation to permit the passage from the blood to the nervous system of larger quantities of spirochæticidal drugs than would otherwise pass over, and possibly also of syphilitic antibodies. If such a result could be demonstrated, either clinically or experimentally, might there not lie herein an explanation of a large part of the benefit derived from the Swift-Ellis treatment and its modifications? Stillman and Swift[19] considered this, among other factors, and showed that irritation of the cat's meninges by various substances did not increase the amount of arsenic in the nervous tissues over that present after simple intravenous injections.

However, this still did not exclude the possibility that, in the neurosyphilitic, intraspinal injections might produce an alteration of permeability to drugs or antibodies. We therefore conceived the idea of a clinical investigation which might demonstrate the efficiency of this procedure in the treatment of neurosyphilis. The method we adopted was briefly as follows: an intraspinal injection of mercurialized serum (Byrnes)[20] was given and followed within 24 hours by an intravenous injection of arsphenamine. Mercurialized serum was chosen because its irritating effect, judging from reactions, was much more severe than that of normal autologous or homologous serum, or of serum arsphenamized *in vivo* or reinforced *in vitro*. The dosage was never more than 0.6 mgm. of mercury, often less, as in our experience this amount was sufficient to produce marked signs of irritation, sometimes lasting a week or ten days; and larger doses, as originally recommended by Byrnes (1.2 to 2.4 mgm.), produced such severe reactions as to interfere with the repetition of treatment. The intraspinal injection was given before the intravenous, so that the highest possible concentration of arsenic might be in the blood stream while the irritation was at its height (from 6 to 24 hours after the intraspinal treatment). In this way a maximum amount of the drug might be expected to enter the nervous tissues. Intraspinal treatments were given in courses, usually of six treatments administered one each week, and each course was followed by 10 to 12 weeks of mercury by inunction. No general mercury treatment was given during the course of intraspinal and intravenous injections.

Certainly, if benefit was to be derived from the (theoretical) increase of permeability of the meninges, it should have been attained by this method, which provided a maximum concentration of arsenic in the blood stream at the time of maximum irritation. In addition there were of course two added factors: the hyperemia of the central nervous sys-

[19] Stillman, E., and Swift, H. F., Jour. Exp. Med., 1915, XXII, 286.

[20] Byrnes, C. M.: J. A. M. A., 1914 (Dec. 19), LXIII, 2182.

TABLE I

Diagnosis	Case	Sex	Age	Duration of syphilis	Duration of neurological symptoms	Previous treatment for neurosyphilis	Treatment given by us: Intraspinal mercury followed by intravenous arsphenamine	Treatment given by us: Spinal drainage and arsphenamine	Treatment given by us: Intravenous arsphenamine alone	Treatment given by us: Months of mercury	Treatment given by us: Duration of treatment, months	Blood Wassermann: Start of treatment	Blood Wassermann: End of treatment	Cerebrospinal fluid at start of treatment: Cells	Globulin	Wassermann	Colloidal gold curve	Cerebrospinal fluid at end of treatment: Cells	Globulin	Wassermann	Colloidal gold curve	Serological result	Clinical result	Remarks
Tabes dorsalis	L.	M.	54	35 yrs.	10 wks.	None.....	11	..	..	6	10	Neg.	Neg.	16	+	1.0 c. c. neg.	0000000000	13	+	1.0 c. c. neg...	1111000000	No change.	Good.	Charcot joint of right first metatarsal healed in three weeks.
	W.	M.	47	20 yrs.	6 mos.	3 doses arsphenamine. Mercury by mouth.	3	..	..	..	1	Pos.	Neg.	26	++	0.2 c. c. pos.	0122210000	22	+	1.0 c. c. neg...	3444321110	Good.	Good.	Relieved of paresthesias in feet one year later.
	T.	M.	37	8 yrs.	3 yrs.	None.....	4	..	..	6	9	Pos.	Pos.	96	+++	0.2 c. c. pos.	5555210000	?	+	0.2 c. c. pos...	2422100000	Bad.	Bad.	Continued down-hill course.
	S.	M.	50	11 yrs.	3 yrs.	5 doses arsphenamine; mercury.	7	..	..	..	5	Pos.	Neg.	47	++	0.2 c. c. pos.	2233210000	64	++	0.2 c. c. pos...	1113310000	Bad.	Good.	Relieved of lightning pains. Ataxia better, has remained in good health for two years.
	Mc.	M.	46	15 yrs.	10 yrs.	None.....	6	3	..	..	5	Neg.	Neg.	22	+	0.4 c. c. pos.	Atypical paretic.	11	+++	0.5 c. c. pos....	0122100000	Bad.	Bad.	Gastric crises worse.
	C.	M.	40	?	2 yrs.	None.....	7	..	..	..	2	Pos.	0.4 c. c. sug. pos.	?	+++	0.2 c. c. pos.	5555210000	?	++++	0.4 c. c. pos...	5433321000	Bad.	Good.	Relieved of lightning pains. Large Charcot joint of right ankle apparently arrested.
General paresis	Na.	F.	18	Juvenile	G. P.	Intermittent arsphenamine and mercury.	5	..	2	4	6	Pos.	Pos.	7	++++	0.2 c. c. pos.	5555522100	5	++	0.2 c. c. pos...	5532100000	Bad.	Bad.	Clinical condition unchanged.
	Hd.	F.	14	Juvenile	G. P.	As with Na.	5	..	2	4	6	Pos.	Pos.	41	+++	0.2 c. c. pos.	5555542100	?	+	0.2 c. c. pos...	5431100000	Bad.	Bad.	Clinical condition unchanged.
	Se.	M.	53	?	5 yrs.	None.....	23	1	12	..	21	Pos.	Neg.	20	+++	0.2 c. c. pos.	5555555520	19	+++	0.2 c. c. pos...	5555432100	Bad.	Fair.	General condition now better than two years ago. Working successfully in an important position.
	C.	M.	18	Juvenile	G. P.	None.....	11	..	..	6	12	Doubtful.	Neg.	58	++	0.5 c. c. pos.	4444210000	6	+	1.0 c. c. neg...	1221000000	Good.	Good.	Relieved of only symptom—intractable bed-wetting.
	R.	M.	27	5 yrs.	3 mos.	None.....	5	1	8	3	6	Pos.	Pos.	84	+++	0.2 c. c. pos.	5555221000	70	+++	0.2 c. c. pos...	5555544310	Bad.	Bad.	Went rapidly down-hill mentally.
	Wi.	M.	39	?	9 yrs.	None.....	19	2	4	..	44	Pos.	Pos.	32	++	0.2 c. c. pos.	5555432100	10	++	0.2 c. c. pos...	5553210000	Bad.	Bad.	Patient held up well until July, 1920, when he began to retrograde mentally. Died Sept. 1920.
Tabo-paresis	Ge.	M.	38	15 yrs. ?	9 yrs.	3 Swift–Ellis treatments 6 years ago.	13	1	5	2	8	Neg.	Doubtful.	26	++++	0.2 c. c. pos.	5521000000	20	++++	0.2 c. c. pos...	5555532000	Bad.	Bad.	Mental retrogression.
	Ha.	M.	40	13 yrs.	18 mos.	Irregular mercury.	7	..	6	9	26	Neg.	Neg.	2	++	0.4 c. c. pos.	Atypical paretic.	37	++	0.2 c. c. pos...	Atypical paretic.	Bad.	Bad.	Ataxia worse.
Cerebrospinal syphilis	Go.	M.	59	?	11 mos.	None.....	3	1	..	..	1½	Neg.	Neg.	38	++++	0.2 c. c. pos.	Paretic.	108	++	0.4 c. c. pos...	Atypical paretic.	Bad.	Good.	Patient working. No recurrence of former numerous mild aphasic attacks.
	Wa.	M.	45	20 yrs. ?	6 mos.	Irregular mercury.	5	1	..	2	3	Neg.	Neg.	146	+++	0.2 c. c. pos.	5444210000	17	++	0.4 c. c. pos...	2224311000	Bad.	Good.	Improvement of recent hemiplegia and relief from severe headache.
	K.	M.	35	4 yrs.	4 yrs.	3 intraspinal injections; irregular mercury.	14	3	..	..	23	Pos.	Neg.	20	+++	0.2 c. c. pos.	Paretic.	6	++	1.0 c. c. neg...	1110000000	Good.	Good.	Severe headaches relieved. Well and working.
	Hi.	M.	33	7 yrs.	3 yrs.	1 intraspinal injection.	8	11	14	5	18	Neg.	Neg.	50	++++	0.2 c. c. pos.	5555311000	7	+	1.0 c. c. sug. pos.	1221000000	Fair.	Fair.	Mental confusion relieved. Severe headaches persist.
	To.	M.	26	5 mos.	10 days.	None.....	13	..	..	4	7	Sug. neg.	Neg.	205	++++	0.4 c. c. pos.	Modified paretic.	16	+	2.0 c. c. neg...	1111220000	Good.	Good.	Severe headaches and all signs of meningeal irritation relieved. Working.
	J.	M.	36	9 yrs.	1 year.	Irregular.....	1	5	10	3	18	Neg.	Neg.	27	+	0.6 c. c. pos.	Paretic.	6	0	1.0 c. c. neg...	0000000000	Good.	Good.	Hemiplegia and syphilitic myelitis much improved.
	Gu.	M.	25	5 mos.	14 days.	None.....	5	1	3	3	5	Neg.	Neg.	28	++	0.4 c. c. pos.	1122100000	6	0	1.0 c. c. neg...	1111000000	Good.	Good.	Perfectly well and working. No further minor aphasic attacks.
	Be.	M.	44	?	8 wks.	None.....	15	..	6	7	18	Neg.	Neg.	16	+++	0.2 c. c. pos.	5555542000	2	+	0.5 c. c. pos...	5554211000	Bad.	Good	Well and working. No further epileptiform attacks.
Asymptomatic neurosyphilis	Z.	F.	29	10 yrs.	.....	None.....	11	1	14	10	17	Pos.	Pos.	28	+++	0.2 c. c. pos.	5552100000	30	+++	0.2 c. c. pos..	5555543210	Bad.	Bad.	Neurosyphilis suspected because of persistently positive blood Wassermann. Since treatment gradual slip in the personality.
	Sr.	M.	29	9 mos.	.....	None.....	5	..	12	2	8	Pos.	Pos.	?	+++	0.2 c. c. pos.	5554210000	?	++	0.4 c. c. doubtful. 1.0 c. c. pos.	5555321100	Bad.	Bad.	Has become moody and unreliable. Secondary syphilis in March, 1920.
	Br.	M.	29	4 yrs.	.....	None.....	6	..	5	3	4	0.4 c. c. sug. pos.	Neg.	17	++	0.2 c. c. pos.	5555511000	6	++	0.4 c. c. pos...	0113331100	Bad.	Good.	No symptoms. Working.

tem, lasting over a period of several days, and the action of mercurialized serum directly. The effects of the former could hardly be evaluated, while the latter was too limited for comparative estimation, owing to the small doses employed.

Our studies are confined to clinical results alone. We have not made determinations of the arsenic content of the spinal fluid. Twenty-five cases were treated. All those cases which might have been expected to improve under routine intravenous treatment alone were excluded. In most instances, such treatment had been thoroughly employed without success.

In Table I are presented the serological and clinical results of the cases treated by this method. The cases are, mainly for the purpose of convenience, classed roughly under the main heads of general paralysis, tabes dorsalis, cerebrospinal syphilis, and asymptomatic neurosyphilis, manifested by laboratory findings alone. This classification is in some instances arbitrary, since we realize the extreme difficulty of making a positive diagnosis of general paresis, on the one hand, or of excluding it absolutely on the other. It will be noted that

TABLE II

Diagnosis	No. of cases	Clinical result		Serological result	
		Good	Bad	Good	Bad
Tabes dorsalis	6	4	2	1	4*
General paresis	6	2	4	1	5
Tabo-paresis	2	..	2	..	2
Cerebrospinal syphilis	8	8	..	15	13
Asymptomatic neurosyphilis	3	1	2	..	3
Total	25	15	10	17	27

*One case, with negative serology at the start of treatment, remained unchanged.

classification is in no instance made on the basis of a so-called paretic gold curve. While we feel that in clinical general paresis this type of gold curve is constant, we cannot subscribe to the view of many clinicians that, given such a curve in the absence of clinical signs, the patient has general paresis, nor are we willing to admit that such a patient will develop general paresis. It is not uncommon to find a paretic gold curve in other forms of cerebrospinal syphilis.

In Table II the results are summarized. Generally speaking, clinical results have been good in about 60 per cent of the cases, but serological results have been poor in practically all groups treated. Much to our surprise the poorest results have been obtained in the group of asymptomatic neurosyphilis, the very class which one might expect to help most easily.

COMPARISON OF OUR RESULTS WITH THOSE OF THE SWIFT-ELLIS METHOD AND ITS MODIFICATIONS

Comparison of these results with those of other workers leads to the conclusion that the method adopted is unsuccessful. Swift[21] reports 37 cases of neurosyphilis, all but 3 tabetics, treated by his own method or by Ogilvie's modification.[22] In 30 of the cases, or 81 per cent, the Wassermann reaction in the cerebrospinal fluid became negative with 1 c. c.; only 2 later relapsed. Nineteen of these cases were also negative with 2 c. c. Of 18 cases which were negative with 1 c. c. or more of fluid, and had been followed from 10 months to 3½ years without treatment, 14 were still negative with 2 c. c.; 2 were negative with 1 c. c. but positive with 2 c. c.; and only 2 had relapsed to positive with 1 c. c. or less. Walker and Haller[23] report practically uniform clinical improvement in 75 cases of neurosyphilis (48 tabes dorsalis, 6 general paresis, 16 cerebrospinal syphilis, and 5 syphilitic meningitis), treated either by the Swift-Ellis method or with salvarsanized serum intraspinally alone. Serological improvement was also noted in practically all cases, but treatment was usually not carried on long enough to effect a serological cure. References of this sort could be multiplied at length.

An incidental comparison of the results of mercurialized and arsphenaminized serum was inevitable from our work. As far as we know such data are largely lacking from the literature. Haller[24] treated two groups of patients with a small number of doses of each with and without intravenous arsphenamine. The amount of treatment given was, in our opinion, too small adequately to judge the permanent effects; but Haller concluded that the average effect on the laboratory findings in the spinal fluid is greater from one dose of mercurialized serum than from one dose of arsphenaminized serum. The clinical improvement seems to have been approximately parallel, but the best results were obtained in active syphilis of the meninges. Inspection of our results suffices to show that the results obtained from mercurialized serum, used by the method we have described, are inferior to results obtained either by ourselves or by others from the Swift-Ellis method.

DISCUSSION

Since our study was begun additional pertinent evidence has accumulated in the literature, and the question of the permeability of the meninges and choroid plexus has been further investigated experimentally. Austrian[25] attempted to produce an experimental meningococcus meningitis in rabbits by intravenous inoculation of the organism, without success. He then repeated the experiment of Flexner and Amoss in an attempt to produce invasion of the cerebrospinal structures from the blood-stream by means of irritation of the meninges. To 20 rabbits, intraspinal injections of 0.5 to 1 c. c. of normal rabbit serum were given, followed in from 30 to 50 minutes by an injection of a standard suspension of meningococcus into an ear vein. Three of these animals developed a typical fatal meningitis, and from the meninges of two others killed one hour after the intravenous injection

[21] Swift, H. F.: Am. J. M. Sc., 1916, CLII, 490.

[22] Ogilvie, H. S.: J. A. M. A., 1914 (Nov. 28), LXIII, 1936.

[23] Walker, I. C., and Haller, D. A.: Arch. Int. Med., 1916, XVIII, 376.

[24] Haller, D. A.: Arch. Int. Med., 1917, XIX, 997.

[25] Austrian, C. R.: Johns Hopkins Hosp. Bull., 1918, XXIX, 183.

meningococci were found in smears. The remaining fifteen rabbits were negative. This demonstrated that the defense mechanism of the meninges of rabbits, while lowered to some extent against the meningococcus, was not so easily disturbed as that of monkeys against the virus of poliomyelitis.

That in other animals and against other organisms a similar phenomenon exists, and that more difficulties are encountered than in the case of poliomyelitis, was shown recently by Weed, Wegeforth, Ayer and Felton.[26] Working with cats, they had great difficulty in finding an organism which was virulent for the cat's meninges but finally discovered one in *B. lactis aerogenes*. When they injected this organism intravenously a meningitis could not be produced unless overwhelming doses were employed, but after certain procedures that modified cerebrospinal conditions they were able to set up an aerogenes meningitis from small intravenous inoculations. In every instance they succeeded in producing this meningitis by spinal drainage, the puncture being made either a few minutes before or within 30 minutes after the intravenous inoculation of a small dose of the organisms.

They assumed this uniformly successful result to be due to the slowing of the blood-stream within the cranium and the consequent cerebral hyperemia. To quote: "A fairly efficient mechanism of adjustment seems to exist within the cranial cavity. Removal of a certain amount of cerebrospinal fluid is followed by a period of low intracerebral pressure, apparently due to the fact that the compensation for the loss of this fluid, while adequate, is not immediate. But certain vascular adjustments occurring quickly upon withdrawal of the cerebrospinal fluid necessarily fill a large part of the space occupied by the evacuated fluid. The chief vascular alteration seems to be more or less extensive venous engorgement with associated slowing of the blood-stream sufficient to account for at least a portion of the space of the fluid withdrawn."

To meet the objection that meningeal infection might be the result of inoculation of the spinal fluid through the medium of the puncture wound, they attempted to reach the same end—venous stasis and cerebral hyperemia—by alternate methods, as follows: (1) Compression of the jugulars for two minutes immediately after the intravenous injection of organisms; (2) stoppage of the heart for two minutes, followed by resuscitation; (3) intravenous injection of 3 c. c. of 30 per cent saline solution immediately preceding the injection of organisms[27]; and (4) an attempt to increase the permeability of the meninges by intraspinal injections of autologous, homologous, or heterologous sera. The first three methods were followed by a typical meningitis in about 50 per cent of the cases. The results were not as uniform as those following spinal puncture, but were still positive enough to refute the objection of the needle puncture as the source of intrathecal infection and to confirm the opinion that the factor producing a meningitis was the cerebral hyperemia and the venous slowing. The results of the attempts to produce infection after meningeal irritation are of particular interest. Thirty-nine cats were injected intraspinally with sera as described, and from four hours to five days later (the interval being prolonged in order to permit the effects of the accompanying spinal puncture to disappear) an intravenous inoculation of *B. lactis aerogenes* was made. Only six of the animals, about 15 per cent, developed a fatal meningitis. In the other 33 the reaction was in all respects similar to that in control animals who had received only the intraspinal injections.

It is of considerable interest to note that in the meningitis produced by Weed and his co-workers, no matter which of the five methods enumerated was used, the first evidences of infection in sacrificed animals, or those which died early in the disease, were localized over the cerebral cortex with later rapid spread thence. This appeared long before any signs of infection in the ventricles—evidence that the passage of organisms was not by way of the choroid plexus, but probably by way of the pericapillary spaces.

In a recent paper Amoss and Eberson[28] record their failure to produce meningococcus meningitis in monkeys by the method of intravenous injection of the organisms followed by spinal drainage or the production of an aseptic meningitis. Repeating Austrian's work with rabbits they were similarly unsuccessful, but state that in one of two rabbits deliberate injury to the spinal marrow with the puncture needle was followed by a spread of the infection to the spinal system.

In immunized monkeys, however, agglutinins of meningococcus and para-meningococcus will make their appearance in the spinal fluid following the setting up of a meningitis which may be either aseptic or produced by intraspinal inoculation of the specific organisms. This phenomenon was observed to bear a quantitative relationship to the degree of irritation induced in the meninges.[29]

The same authors, replying to the objection of Herrick[30] that intraspinal injections of antimeningococcus serum in early meningococcemia in man might promote the passing over of organisms from the blood to the cerebrospinal fluid, state that, while this is true for the meningeal irritation produced by other means in poliomyelitis, it is distinctly inhibited when specific immune serum is employed.

This suggests the possibility of a selective meningeal activity hitherto unmentioned which may have to be considered as a factor not only in the Swift-Ellis method for the treatment of neurosyphilis, but more especially in methods which depend for their success on the (theoretic) permeability of the meninges.

The apparent inconsistencies in these experimental results make correlation of the data difficult, if not indeed impossible. We must assume that there exist variations in the integrity and resistance of the meningeal defense mechanism of differ-

[26] Weed, L. H., Wegeforth, P., Ayer, J. B., and Felton, L. D.: Monographs of Rockefeller Institute for Med. Research, No. 12, March 25, 1920, 57.

[27] Weed, L. H., and McKibben, P. S.: Am. J. Physiol., 1919, XLVIII, 512.

[28] Amoss, H. L., and Eberson, F.: Jour. Exp. Med., 1919, XXIX, 605.

[29] *Loc. cit.*, 597.

[30] Herrick, W. W.: Arch. Int. Med., 1918, XXI, 541.

ent animal species, and that this mechanism in a given species exhibits variable degrees of susceptibility to organisms and other substances under the same conditions. For example, the virus of poliomyelitis can easily be transferred from blood-stream to spinal fluid in monkeys by spinal irritation, but in rabbits and cats the *Meningococcus* and *B. lactis aerogenes*, respectively, are only exceptionally passed over in similar experiments. On the other hand, in monkeys intravenously inoculated with the virus of poliomyelitis, spinal drainage was not sufficient to carry over the infection, while in cats the same procedure produced a *B. lactis aerogenes* meningitis in every experiment. It is therefore impossible, in experiments of this sort, to predict the effect of any procedure designed to affect the meningeal defense against any organisms or substances in a given animal when the prediction is based merely upon similar experiments in an animal of another species.

Thus it cannot be argued that spinal drainage, or the production of aseptic meningitis, or similar procedures will cause alterations in the human meningeal defense mechanism, facilitating the passage of drugs from the blood-stream to the cerebrospinal fluid, on the basis of similar phenomena in animal experiments. Nor should we be justified in assuming that the same results obtained by these procedures in normal human individuals would be obtained in cases of neurosyphilis where meningeal conditions are already altered by the disease processes. It might be expected that the lesions present, to say nothing of alterations in the normal pressure relations, might cause marked changes in the functional activity of the defense mechanism. It is conceivable that in one case of neurosyphilis meningeal irritation might increase the permeability of the complex, in another leave it unaltered, and in a third even decrease it.

Investigations along these lines in the human subject, and especially the neurosyphilitic, are few. Regarding the passage of syphilitic antibodies it must be borne in mind that there is little definite knowledge on this point. Kolmer [31] and others have demonstrated agglutinins for *T. pallida* in immunized animals and Kolmer, Broadwell, and Matsunami [32] found that the sera of syphilitics in the later stages of the disease agglutinated culture pallida in about 84 per cent of the sera studied. Agglutinins in the cerebrospinal fluid were absent in the few cases tested. We have been unable to find references to studies calculated to demonstrate the presence or absence of agglutinins after meningeal irritation. We were successful in an attempt to demonstrate the passage of hemolytic amboceptor from the blood to the cerebrospinal fluid after meningeal irritation in only one of 12 cases.

As for arsenic, Mehrtens and McArthur [16] found that intravenous injection of arsphenamine resulted in a positive test for arsenic in 43 per cent of the spinal fluids withdrawn one hour later, and that the procedure of spinal drainage did not increase this percentage. When the intravenous injection was preceded six or eight hours by an intraspinal injection of the patient's own serum, 92 per cent of the cases gave a positive arsenic test in the fluid, and the average amount of arsenic present was three times as great as in the controls. Hall and his associates,[33] using a similar technique, found that preliminary intraspinal injections did not increase the percentage of positive tests for arsenic nor the amount of the drug present. They criticize the work of Mehrtens and McArthur on the grounds that the latter detected the presence of arsenic in amounts smaller than the delicacy of the test used would permit.

In a recent paper Dercum [2] states that spinal drainage is productive of as good, if not better, results than any method of intraspinal therapy. He contends that nutrition of the central nervous system is carried on by the perivascular, pericapillary, and perineuronal lymph spaces of the brain and cord; and that absorption of the cerebrospinal fluid and of various substances introduced into it takes place, in small part, at least, by way of these lymph channels. In this connection Sabin [34] and her co-workers were unable to demonstrate the existence of lymphatics in the central nervous system; and Dandy and Blackfan [24] concluded from their experiments with phenolsulphonephthalein that the lymphatics play no part in the absorption of cerebrospinal fluid.

Dercum objects to intraspinal medication because substances introduced into the cerebrospinal fluid rapidly disappear into the general circulation; and because, even if they did not disappear, they could not penetrate to the diseased cells of the parenchyma. Dandy and Blackfan [24] have shown for internal hydrocephalus, and Mehrtens and West [35] for other diseases of the central nervous system, notably neurosyphilis, that the time of appearance in the urine of phenolsulphonephthalein introduced subdurally is enormously prolonged over the normal. The total excretion, normally complete in about six hours, was also very much but not uniformly prolonged. This being true for a dye as diffusible as phthalein, it is reasonable to assume that the execretion of spirochæticidal substances introduced is also much prolonged and that such substances may remain in contact with the diseased meninges for several hours at least.

That substances introduced subdurally can, under certain circumstances, reach the parenchymatous cells of the nervous system, is demonstrated by the results of treatment in poliomyelitis. The pathology [36] of poliomyelitis consists essentially of an acute interstitial meningitis, followed by extensive perivascular infiltration entering the parenchyma of the cord, and ultimately involving particularly the anterior horn cells and the posterior root ganglia. Brain, cerebellum and medulla

[31] Kolmer, J. A.: Jour. Exp. Med., 1913, XVIII, 18.

[32] Kolmer, Broadwell, and Matsunami: Jour. Exper. Med., 1916, XXIV, 333.

[33] Sabin, F.: Johns Hopkins Hospital Reports, Monographs, New Series, No. V, 1913.

[34] Dandy, W. E., and Blackfan, K. D.: Am. J. Dis. Children, 1914, VIII, 406.

[35] Mehrtens, H. G., and West, H. F.: Arch. Int. Med., 1917, XX, 575.

[36] Peabody, F. U., Draper, G., and Dochez, A. R.: Monographs of the Rockefeller Institute for Medical Research, 1912, No. 4, 18.

may be similarly involved. Amoss and Chesney [27] have demonstrated the curative effect of combined intraspinal and intravenous injections of immune poliomyelitis serum. The mechanism by which benefit is effected—whether it be by direct action of the serum on the virus of poliomyelitis within the diseased tissue, or whether the irritation of the intraspinal injection opens the pathway for the passage of immune bodies from the blood—is here beside the point. The fact remains that in some way the parenchyma of the nervous system is reached and benefit ensues.

Parenchymatous neurosyphilis is practically always associated with syphilitic disease of the meninges, and in a large proportion of neurosyphilitics meningitis is the principal if not the sole disturbance. It is these very cases—early tabes dorsalis, cerebrospinal syphilis, or very early asymptomatic neurosyphilis—in which the greatest benefit is to be derived from intraspinal therapy.

[27] Amoss, H. F., and Chesney, A. M.: Jour. Exp. Med., 1917, XXV, 581.

CONCLUSIONS

1. Intraspinal therapy is a necessary and rational adjunct in the treatment of neurosyphilis in cases which fail to respond to routine antisyphilitic treatment.

2. The mode of action of intraspinal medication does not depend upon increased permeability of the meninges.

3. Aseptic meningitis produced by intraspinal injection of irritants may prove an untoward rather than a beneficial factor in the treatment of neurosyphilis.

MONONUCLEAR LEUCOCYTOSIS IN REACTION TO ACUTE INFECTIONS

("INFECTIOUS MONONUCLEOSIS")

By Thomas P. Sprunt and Frank A. Evans

(From the Division of Clinical Pathology of the Medical Clinic, The Johns Hopkins University and Hospital)

A mononuclear leucocytosis in children is not unusual, and when it occurs is a simple lymphocytosis showing almost exclusively normal lymphoid forms or cells varying but slightly from them in morphological characteristics. In adults also one may encounter occasionally a mononuclear leucocytosis, but the picture presented is different from that seen in children in that the increase in leucocyte count is due largely to pathological forms of diverse morphology, probably all lymphoid in origin but not proven so. Such a blood picture may be seen in a variety of conditions, but among them there are some that show not only the same blood picture but other signs and symptoms so much alike that they seem to constitute a group by themselves.

During the past few years we have observed several cases in adults presenting the symptoms of an acute infection, a moderate enlargement of the lymph nodes and of the spleen, and a mononuclear leucocytosis instead of the more usual increase in the polymorphonuclear leucocytes. Similar cases have been described by Türk,[1] Lüdke,[2] Marchand,[3] Cabot,[4] Sanders [5] and others, and most of these authors emphasize the resemblance of such cases to acute leukæmia. Türk considered this group of cases as a key to the understanding of acute leukæmia and upon it are based arguments for the infectious nature of the acute leukæmias by those who favor that theory. Although these reports have been in the literature for some time, such cases are not very generally recognized and each new one is apt to give rise to grave apprehension of the onset of a leukæmic state. Hodgkin's Disease, also, has usually been suggested as a possible diagnosis during the observation and study of cases of this series. The close similarity to each other in symptomatology, in physical findings, and especially in hæmatology, gives these cases a well-defined position as a fairly clear-cut clinical group, whether or not they may form an entity from the viewpoint of etiology. A better appreciation of this syndrome is desirable, not only for the sake of accuracy in diagnosis but also because in this relatively benign affection a favorable prognosis may be given.

CASE I

H. C. Medical No. 31625. White woman, unmarried. Age 23 years. Medical student. Admitted to the hospital October 24, 1913. Discharged November 18, 1913. Acute febrile disease without local manifestations except marked lymphocytosis and slight enlargement of lymph nodes and spleen. Recovery.

Complaint.—Headache and backache.

Family History.—Unimportant.

Personal History.—The patient had had measles and scarlet fever in childhood, smallpox in 1907—mild, and frequent attacks of inflammatory rheumatism, the last one four years ago. Until the tonsils were removed five years ago, there were repeated attacks of tonsillitis. Otherwise the personal history was negative.

Present Illness.—The patient had been feeling badly for several days, but was not sick. The day before admission there appeared suddenly an occipital headache and chilly sensations. When the patient was admitted to the hospital she had headache, aching in the back and some pain in the left side.

Physical Examination.—On admission (summary): T., 102°; P., 80 per min.; R., 26 per min. The patient was a little dull. Her face was flushed. There was slight photophobia and conjunctivitis. The thyroid isthmus was enlarged but there was no bruit. At the apex of the right lung the breath sounds were harsher and expiration was longer than on the left. The percussion note on the right at the apex was a little shorter than on the left. Relative cardiac dulness extended 11.5 cm. to the left and 4 cm. to the right of the mid-sternal line. The first sound at the apex was slightly booming in quality and was followed by a

well-marked systolic blow. There was general tenderness over the abdomen but no resistance or spasm, and the right kidney was palpable. The liver was 2 cm. below the costal margin in the mid-clavicular line. The spleen was not palpable.

On the next day, chains of firm, discrete, slightly tender lymph nodes were noted in the left anterior and posterior cervical triangles. On October 30, one week after the onset, a pharyngitis appeared and there was moderate enlargement of lymph nodes in all the cervical regions and in the axillæ, slight impairment of the percussion note over the manubrium and an enlarged area of splenic dulness which reached nearly to the costal margin. The edge of the spleen could not be felt. Although the blood had been repeatedly examined for malarial parasites both in fresh and in stained preparations, the abnormal differential formula of the leucocytes was not noted until this day, when a well-marked lymphocytosis was present.

Blood.—Numerous *examinations for malarial parasites* were negative. *Blood cultures* and *Wassermann reaction* were negative. The *bleeding time* was slightly prolonged. The record of the blood examination is shown in Chart I.

Lymph Nodes.—A chain of nodes was removed from the neck on October 11. They were soft, friable and on section more nearly uniform than the normal tissue.

1. A piece was ground up in salt solution and injected into the peritoneal cavity of a guinea-pig with negative results.

2. Cultures were made on blood agar and on Loeffler's serum and incubated for many days without growth.

3. Sections were prepared for histological study and examined by Professors Welch and Whipple. The lymphoid tissues showed no follicles and no increase in fibrous tissue. The lymph cords were distinct and mitotic figures numerous. The sinuses were filled with many lymphoid and some endothelial-like cells.

BLOOD CHART.—CASE I

Date	10-30-13	11-4-13	11-6-13	11-10-13	11-17-13	12-6-13	1-6-14	1-7-14	11-6-14	3-26-15	4-30-20
R. B. C.	5,072,000	....	....	....	5,376,000	....	....	....	5,104,000	5,400,000	4,892,000
Hb. %	90	....	92	....	96	....	....	....	90	90	75
W. B. C.	10,000	17,500	13,920	9,800	9,200	9,000	8,700	13,500	6,800	6,000	5,200
P. M. N. %	24.	....	19.3	14.3	26.	21.2	46.6	75.	63.5	56.	65.
P. M. E. %	.8	....	.0	....	.3	.4	.3	....	....	....	1.
P. M. B. %	.4	....	.3	.3	.6	.8	.3	.3	1.	1.	1.
Small lymphocytes %.	57.2	....	28.6	66.6	62.6	69.2	44.6	16.6	26.	17.	16.
Large lymphocytes %.	14.	....	36.	15.6	2.6	6.	4.3	3.6	....	8.	10.
Large mononuclears %.		....	1.6	2.	.6	1.2	3.	2.6	2.5	5.	3.
Transitionals %	1.6	....	4.	....	2.	....	.6	.6	4.	2.5	2.
Unclassified %	.8	....	10.	1.	5.	1.2	....	1.	3.	10.	2.
Myelocytes %	.8	....	.6	....	....	....	....	....	....	....	....
Clinical condition.	Febrile.	....	Subjectively much improved.	Convalescent.	Convalescent 2 days before discharge from hospital.	Convalescent.	Apparently well.	Acute tonsillitis.	Well.	Indisposition with tender cervical lymph nodes.	Five years after recovery.

On November 4, the white blood count reached it highest point, 17,500, and the cervical nodes had increased in size. The spleen was felt on November 10. On November 6, the temperature had fallen almost to normal and subjectively the patient was much improved. Convalescence was uneventful. When discharged from the hospital there were still many slightly enlarged nodes in the neck and axillæ, slight impairment of the percussion note over the manubrium, and increased splenic dulness. The leucocytes numbered 9200 with the lymphocytes 65 per cent. The systolic blood pressure was 115 mm. Hg., the diastolic 75. When the temperature was high, the pulse rate varied from 100 to 120 per minute.

Laboratory Data.—There was no *sputum*. A *throat culture* on November 4, when there was a complaint of sore throat, showed only the usual flora. *Urine* and *fæces* were normal.

The *von Pirquet tuberculin* test was considered faintly positive on November 2,, but on repetition on November 19 was quite negative.

An *X-ray examination* of the thorax revealed nothing unusual. There was slight thickening of the mediastinal tissues and a moderate chronic infiltration of both lungs, more marked on the right.

Neither eosinophiles nor giant cells were found. While no diagnosis was made, it was agreed that such a picture might be found in a lymphatic leukæmia.

Subsequent Course.—The patient has been under observation for six years. Examinations of the blood were made at intervals as shown in the table. On January 6, 1914, the polymorphonuclears and mononuclears were about equally divided. Ten days later, during a mild tonsillitis, the blood picture showed the usual polymorphonuclear reaction to such infections. One year after this illness her general health was excellent, lymph nodes in the neck and axillæ were just palpable, there was no demonstrable splenic enlargement and the heart was quite clear. The blood was normal.

During the six years since the illness reported here the patient has worked hard as a medical student, interne and laboratory worker. She is at present entirely normal and shows a normal blood picture.

The second case differs from the first in that it presented a more prolonged and less acute febrile period.

CASE II

R. L. R. Medical No. 34068. White man, unmarried, age 24 years. Medical student. Admitted to hospital April 20, 1915. Discharged June 10, 1915. Febrile disease of about 10 weeks duration with lymphocytosis and enlarged spleen. Recovery.

Complaint.—Chills, fever, loss of weight.

Family History.—Unimportant.

Personal History.—The patient had had measles, mumps and whooping-cough as a child. Otherwise negative.

Present Illness.—The present illness began insidiously about one month before he entered the hospital, and was considered an ordinary attack of "La Grippe" because of the "cold in the head," headache, soreness in chest, neck and back, and general malaise. For three days there was a chill each evening about 7 p. m. The temperature was not taken. After three days in bed and a few doses of aspirin and quinine he felt well, returned to work and was apparently quite normal for four days. The symptoms then returned, soreness, anorexia, a chill each day at 7 p. m. and fever which increased a little each day until it reached 102° at 10 p. m. two days before admission to the hospital. There was slight constipation, no cough, no pain in the abdomen or chest. Quinine had no apparent effect.

Physical Examination.—On admission (summary): T., 101° F.; P., 112 per min.; R., 18 per min. The patient was a well-nourished young man. He looked sick. The tonsils were not enlarged or inflamed. The lymph nodes under the angles of the jaw were palpable. The chest was clear. The abdomen was distended. The spleen was palpable just below the costal margin. It had a rounded edge, was firm and rubbery. The thyroid isthmus was palpable and there was fulness over the lobes. There was some tremor of the fingers and sweating of the hands.

Laryngoscopic examination (Dr. Crowe) was negative except for chronic infection of the right tonsil.

Laboratory Data.—The *urine* and *stools* were normal. *Calmette 1 per cent tuberculin reaction* was negative. *X-ray examination* of the thorax showed clouding of both apices, slight infiltration of both upper lobes and slight pleuro-diaphragmatic adhesions on the right side. X-rays of the paranasal sinuses were negative.

Blood.—*Cultures* from the blood on April 20 and on May 25 were sterile. The *Wassermann reaction* was negative. Repeated tests for agglutinins for *B. typhosus* and *B. paratyphosus* were negative. *Malarial parasites* could not be found either in ordinary smears or in thick films prepared by the Ross method.

There was a continuous fever for the first three days and then it became intermittent for about three weeks, reaching 101° F. in the evening and about 99° F. in the mornings. It then became remittent and the patient was discharged at the end of seven weeks with a slight evening fever (99° F.).

The spleen was palpable throughout the patient's stay in the hospital and was palpable on discharge. The enlargement of the glands had disappeared.

This patient finished his course in medicine, served a term as medical officer in the army and now, four years after this illness, is a practising physician.

The main interest is in the blood picture. See Chart II.

CASE III

H. B. G. Medical No. 37257. White woman, unmarried. Age 29 years. Medical student. Admitted to hospital February 5, 1917. Discharged February 19, 1917. Diagnosis: Acute infection, pharyngitis, adenitis.

Complaint.—Headache and general malaise.

Family History.—Unimportant.

Personal History.—The patient has had measles, mumps and varicella in infancy, malaria at three years of age, and for years an annual attack of tonsillitis.

Present Illness.—The present illness began about three weeks before the patient's admission to the hospital with headache, swelling of the glands of the neck, and a slight cough. She was kept in bed at home under supervision. Finally, the muscles of the neck and shoulders became sore and tender, the cervical glands became tender also and the patient was admitted to the hospital.

BLOOD CHART.—CASE II

Date	4-20-15	4-25-15	5-10-15	5-31-15	6-8-15
R. B. C.	5,328,000	....	....	....	4,184,000
Hb. %	88	....	....	....	91
W. B. C.	6,620	7,000	6,800	9,320	7,600
P. M. N. %	40.8	....	....	26.6	28.8
P. M. E. %	.0	....	....	.0	.0
P. M. B. %	0.4	....	....	.0	.4
Small Lymphocytes %	34.	....	....	56.7	49.6
Large Lymphocytes %	18.	....	....	12.7	3.6
Large Mononuclears %	....	....	....	....	1.2
Transitionals %	6.8	....	....	4.0	7.6
Unclassified %	....	....	....	....	8.8
Myelocytes %	.0	....	....	.0	....

Physical Examination.—On admission (summary): T., 99.5°; P., 100 per min.; R., 28 per min. She was a well-nourished young woman and looked ill. The tonsils were small, adherent and showed many small crypts. The pharynx was injected and showed a rather marked lymphoid hyperplasia. The posterior and anterior cervical, submaxillary, axillary and inguinal glands were palpable, firm and tender. The chest was clear and the heart and abdomen negative. The spleen was not felt. The *urine* examination was negative.

BLOOD CHART.—CASE III

Date	1-22-17	1-24-17	2-5-17	2-17-17
Total W. B. C.	11,800	10,000	10,400	17,280
Differential:				
P. M. N. %	59	45	42.	43.4
P. M. E. %	1	2	4.8	4.4
P. M. B. %	0	0	.0	.2
S. L. %	12	27	20.8	22.2
L. L. %	12	13	23.2	20.2
L. M. Transitionals %	16	9	8.	8.2
Unclassified %	0	0	.0	1.4

There was an intermittent fever for four days after admission, reaching 100° F. in the evenings and being normal in the morning. For the following 10 days while she remained in the hospital the temperature was normal.

Blood.—See Chart III.

Since her discharge from the hospital, the patient has remained well. She finished her course in the medical school and is now an interne in a hospital.

CASE IV

S. H. H. Medical No. 42775. White man, unmarried. Age 25 years. Medical student. Admitted to hospital October 17, 1919. Discharged November 26, 1919. Diagnosis: Adenitis, infectious mononucleosis.

Complaint.—Headache and swelling of the glands at the angles of the jaw.

Family History.—Unimportant.

Personal History.—The patient has had mumps, measles, and whooping-cough in childhood and an occasional sore throat. He was in the hospital in November, 1917, with a chronic bronchitis. Tuberculosis was considered at this time, but was fairly definitely excluded.

Present Illness.—Three weeks before his admission to the hospital the patient noticed while shaving that the glands under the angles of the jaw were swollen. A few days later he began to have headache and general malaise which gradually increased in intensity until his admission to the hospital.

Physical Examination.—On admission (summary): T., 100.6°; P., 80 per min.; R., 22 per min. The face was slightly flushed, the skin moist and hot, the pharynx injected and showing a slight muco-purulent exudate over the posterior pharyngeal wall. The tonsils were slightly enlarged and hyperæmic, but without exudate. The posterior and anterior cervical, axillary, inguinal, and epitrochlear glands were palpable, of a rubbery consistence, and were slightly tender. The chest showed signs of fibrosis at the right apex. The heart was normal. The spleen was palpable one finger's breadth below the costal margin.

The *urine* and *stool* examinations were negative. The *Wassermann* test, a *blood culture* and an *X-ray* of the chest were negative. The *throat culture* showed a non-hemolytic streptococcus.

Several days after admission the patient developed pus crypts in the tonsils.

A *cervical gland* was removed for study on October 20, 1919.

Report by Dr. Martzloff.—"Section of lymph gland in which normal lymphoid architecture is lost. The lymph sinuses are engorged. There are many large cells with round or oval nuclei that are pale-staining. Numerous polymorphonuclear neutrophile and transitional cells, and occasional eosinophile cells are seen. There is an increase in lymphocytes. No areas of necrosis or invasion are present. No giant cells or Dorothy Reed cells are seen. Impression: Lymphadenitis."

Report by Dr. Bloodgood.—Dr. Bloodgood agreed with the above report and raised the question if this might be a very early Hodgkin's Disease, earlier than has ever before been studied histologically.

Temperature readings showed an intermittent fever for 16 days, reaching 101° F. in the evening, becoming normal on the seventeenth day in the hospital; and then, except for several days when there was one-half degree elevation, remaining normal.

Blood.—See Chart IV.

Since his discharge from the hospital more than six months ago, the patient has been well. He now has a slight general glandular enlargement, but his spleen is no longer palpable and the blood picture has become normal.

CASE V

White man, unmarried. Age 28 years. Banker. This patient was a private patient of Dr. Lawrence Getz, who gave the authors all the clinical data and supplied blood specimens for study.

Complaint.—Headache and general malaise.

Family History.—Unimportant.

Personal History.—The patient had a guillotine tonsillectomy in childhood. Otherwise the history is unimportant.

Present Illness.—Three days after having been chilled at a football game the patient went to bed with fever and general malaise, headache, anorexia, and photophobia. Three days later rigidity of the neck developed. At this time on examination the spinal fluid was normal. Six days after the onset the patient developed a sore throat involving uvula, soft palate, pharyngeal walls and tonsillar tissue. At this time there was tenderness over the sides of the face.

Physical Examination.—At the onset there was flushing of the face, fever, prostration, slight conjunctivitis, and some little swelling of the lower face and neck. The heart and lungs were clear. The abdomen was negative.

The rigidity of the neck developing three days later was probably associated with the tenderness and swelling of the glands and tissues of the neck. The injection of the uvula, soft palate, pharyngeal walls and bits of tonsillar tissue was present six days after onset.

Early in the illness the anterior and posterior cervical and the axillary glands were palpable, slightly enlarged, firm and a little tender. The spleen became palpable several finger-breadths below the costal margin, was firm and had a rounded edge. It remained palpable throughout the course of the illness.

The *urine* showed a faint trace of albumin and a few granular casts. The *spinal fluid* was normal. Two *blood cultures* were negative.

The temperature showed remittent fever for a few days and then became intermittent in type. The highest evening temperature was 102.8° F. shortly after the onset. After 17 days the temperature became normal for the whole 24 hours and remained normal until recovery was complete.

Blood.—See Chart V.

Since recovery the patient has been well and has been carrying on his usual occupation. Examination on April 11 showed that there was no glandular enlargement and the spleen was not palpable. The blood picture was normal.

Through the courtesy of Dr. Barker the following case from his private clinic was studied:

CASE VI

A young woman, Medical No. 5905, 20 years of age, from a distant state, was observed in October, 1919, during convalescence from an acute infection associated with lymphadenopathy and lymphocytosis.

Complaint.—At this time was of fatigue and drawing sensations in the left leg, especially at night.

Past History.—The patient's health has been good with the exception of tonsillitis because of which a tonsillectomy was done two years ago. She suffered from occasional headaches, rather frequent colds, constipation and dysmenorrhea.

Present Illness.—The present trouble began about two months before and was characterized by asthenia, malaise, fever for three weeks with the temperature ranging from 99° to 102°, a general glandular enlargement and a leucocytosis of 17,000 with the following differential count of 500 cells: P. M. N., 16.4 per cent; P. M. E., 0.4 per cent; P. M. B., 0.2 per cent; small lymphocytes, 77.5 per cent; large mononuclears, 1.6 per cent; transitionals, 3.6 per cent.

In the examination in Dr. Barker's clinic three or four weeks after the cessation of the fever the essential findings, outside the blood and hematopoietic system, were undernutrition to the extent of about 15 pounds; a thickened thyroid isthmus and pulse rate of 100; unerupted upper third molars; gastric hypoacidity, slight tenderness in the right lower quadrant of the abdomen, overfilling of the cæcum and spasticity of the colon.

The spleen was not palpable nor apparently enlarged on percussion.

There was very slight general lymph glandular enlargement, including the cervical, axillary, epitrochlear, peribronchial and

BLOOD CHART.—CASE IV

Date	10-17-19	10-20-19	10-21-19	10-22-19	10-23-19	10-24-19	10-26-19	10-29-19	11-3-19	11-10-19	11-15-19	11-21-19	12-22-19	4-5-20
R. B. C.	5,240,000	....	....	5,560,000	....	....	....	6,072,000	....	5,600,000	5,760,000	5,968,000	....	5,744,000
Hb. %	98	....	....	98	....	....	....	98	....	100	100	100	....	100
W. B. C.	7,800	18,820	18,560	20,800	17,400	10,820	8,160	11,240	8,020	8,400	12,700	9,800	9,000	8,900
P. M. N. %	22.5	21.5	29.5	27.	30.	34.5	19.	49.	48.5	59.	56.	59.	66.5	75.
P. M. E. %	2.5	1.5	0.5	2.0	4.0	4.5	1.0	9.	5.0	6.0	9.0	12.0	6.0	5.
P. M. B. %	.0	.0	.0	.0	.0	.0	1.	1.	1.5	2.0	.0	.0	.0	0.
S. L. %	14.5	19.0	42.	45.5	40.	49.	66.	26.	34.	25.	25.	25.	3.5	8.
L. L. %	.0	.0	24.	21.5	22.	9.5	7.5	11.	6.5	4.5	4.	1.	13.5	7.
L. M. %	13.5	8.0	3.0	3.0	2.0	1.0	1.0	3.0	3.0	1.5	1.0	1.0	3.5	0.
Trans. %	9.5	7.0	1.0	1.0	.0	1.0	1.0	1.0	1.5	2.0	5.0	2.0	3.5	2.
Unclass. %	37.5	43.0	....	....	....	....	1.0	....	....	....	....	....	....	3.
Myelocytes %	....	....	....	....	2.0	....	1.0	....	....	....	....	....	....	....
Myeloblasts %	....	....	....	....	....	1.0?	....	....	....	....	....	....	....	....
Remarks	On admission.	Pus crypts in tonsils.	....	Highest fever recorded.	....	....	....	Slight evening fever.			Afebrile.			4 months after recovery.

BLOOD CHART.—CASE V

Date	11-26-19	11-29-19	12-3-19	12-5-19	12-7-19	12-9-19	12-11-19	12-14-19	4-11-20
R. B. C.	....	4,516,000	5,120,000	4,672,000	4,172,000	3,800,000	4,400,000	4,656,000	4,920,000
Hb. %	....	103	....	....	....	....	....	....	98
W. B. C.	6,500	6,200	17,120	18,420	18,460	11,825	9,700	6,600	5,080
P. M. N. %	....	49.6	23.8	28.5	24.0	28.0	32.0	22.1	56.
P. M. E. %	....	3.2	2.0	0.7	1.0	1.0	0.7	0.7	7.
P. M. B. %	....	.0	.0	0.7	.0	0.5	.0	0.7	1.
S. L. %	....	23.0	12.3	21.4	22.0	13.5	10.0	11.5	19.
L. L. %	....	17.6	43.8	28.5	36.0	48.0	49.2	50.4	6.
L. M. %	....	3.2	11.5	7.2	5.0	9.	7.4	0.7	3.
Trans. %	....	2.4	6.	7.2	4.0			13.7	5.
Unclass. %	....	.0	.0	.0	7.0	.0	.0	.0	3.
Myelocytes %	....	.0	.0	5.0	1.0	.0	.0	.0	....
Remarks	....	Rigidity of neck. Lumbar puncture.	Pharyngitis. Swelling of neck and face.	....	....	....	Temperature normal.	....	4 months after recovery.

inguinal groups. A gland was excised from the region of the scapula, histological preparations were made and the following reports received:

From Dr. W. G. MacCallum.—"The lymph gland is not especially enlarged; in general its architecture is maintained. One can see the peripheral sinuses quite plainly. There is, however, a great enlargement of the lymphoid tissues proper so that the interior of the gland tends to become a solid mass. The distinction between the germinal centers and the peripheral part of the lymph cord can still be made out. The sinuses contain many free cells, but are not packed with them. Most of these are small cells with deeply stained round nucleus and, although with this fixation practically nothing can be seen of their cytoplasm, they look like lymphocytes. There is some infiltration of these same cells in the capsule of the gland and there are lymphatics there which are filled with them. In the periphery the lymphoid cells are practically pure around the margin of the lymph cord, while the center is made up of larger and paler cells. There is one quite large area which seems to be more diffusely made up of these larger cells, which might be called reticulum cells. Among these are a few lymphoid cells, most of which are fragmented.

"There is nothing about this gland which would allow anyone to make a definite diagnosis. It appears, however, that several things can be excluded. It has not the structure of Hodgkin's Disease; there is no such tumor growth or infiltration as would suggest strongly a lymphosarcoma. The condition is consistent with the diagnosis of lymphocytic leukæmia, but, if so, it must be a very early stage or else in a period of recovery."

From Dr. Joseph Bloodgood.—"There is nothing in the sections that would allow a positive diagnosis. The histology of the gland is not normal. It suggests an acute rather than a chronic process.

"There is no endothelial hyperplasia or increase of stroma. There are no tubercles or giant cells and no definite Dorothy Reed cells.

"The marked features are increased vascularity of the capsule and apparently proliferation of the lymphoid cells, which are a little larger than in a normal resting gland. On the whole there is slight obliteration of the stroma of the gland and endothelial-lined spaces.

"One could not exclude lymphosarcoma. In leukæmia the lymph glands have this appearance, but when lymph glands are removed for other acute infections not pyogenic, they are difficult to differentiate from the gland in sarcoma or leukæmia.

"The diagnosis in a case of this kind must rest upon the blood picture."

Blood.—On examination showed:

(a) R. B. C., 4,496,000. Hb., 85 per cent. W. B. C., 9000 with the differential formula: P. M. N., 56.4 per cent; P. M. E., 0; P. M. B., 0.8 per cent; S. M., 34 per cent; L. M. and T., 8.0 per cent. The red cells were a little pale, otherwise normal; the platelets were normal in number and no abnormal cells were seen.

(b) The *Wassermann* reaction was negative.

(c) The *blood culture* was negative.

All these cases were in young adults. Each ran a febrile course. In two the onset was rather sudden; in the other four there was a prodromal period of three or four weeks. The symptoms were those of an obscure infection without marked localization in two cases. Of the others two showed definite evidences of upper respiratory tract infection and two symptoms suggesting, in addition, a myositis of the neck and shoulder region. Two patients had conjunctivitis and photophobia. All showed enlarged and tender cervical glands and five of the six had, in addition, enlarged and slightly tender glands in the axillary and inguinal regions. In four cases the spleen was palpable but in none was it markedly enlarged; when palpated it felt hard and rubbery. In none of these patients could tuberculosis be demonstrated and, although three showed a slight enlargement of the thyroid gland, there was no evidence of active thyroid disease or status thymico-lymphaticus. The temperature in the five febrile cases followed from the onset, was remittent or intermittent with a rise to 101° to 103° in the evening. One case showed an evenly elevated temperature for three days, after which the intermittent course appeared. The average duration of fever was between two and three weeks.

The urine of one patient showed albumin and casts, but urine examinations in the other cases were negative. Stool examinations were negative in all. None showed a positive Wassermann test. In the four cases in which blood cultures were made, they were negative. Throat cultures were made in two of the cases, one of which showed a non-hemolytic streptococcus. Culture of the cerebrospinal fluid in one case was negative. Animal inoculation of a gland in one case failed to disclose a definite etiological agent.

The blood picture in all the cases observed from the beginning (Cases I to V, inclusive) was the same, showing variations hardly even in minor points. For the first few days the total white blood cell count was normal or only slightly increased. Then followed a leucocytosis of from thirteen to twenty thousand cells per cubic millimeter. The differential counts showed that the percentage of mononuclear elements was increased and that when the leucocytosis occurred it was due largely to an increase in these cells. The small lymphocytes and to a less extent the cells of the large mononuclear-transitional group (the granular mononuclears of normal blood)[6] were increased, but the chief changes were due to the presence of those cells designated (for want of a better name) by the term "large lymphocytes." Under this heading were included all mononuclear cells seen that were not small lymphocytes or those of the large mononuclear-transitional group. Among these were cells (see plate) differing from a true lymphocyte only in that they had a finely reticulated, purplish-staining nucleus.* Others with the same type of nucleus were large and had an abundant protoplasm which was stained either a deep, dark blue or a clear, pale blue. There were large cells with deeply staining blue-black, pyknotic nuclei, showing the same variations in the protoplasm as the cells with the finely reticulated, purple-staining nucleus. Some few showed an occasional azurophile granule, but these were the exception. An occasional cell showed the clover-leaf, so-called Rieder nucleus. In other words, all types of pathological lymphocytes, some resembling Türk's irritation forms, were to be seen. None of those so studied showed granules with the Ehrlich stain or contained an oxydase ferment as demonstrated by Graham's[7] method. Just what is the significance of these cells cannot be stated at present, but they are generally accepted as lymphoid in origin. The red blood cell counts, hemoglobin determina-

* Wilson's modification of the Romanowsky stain was used for the routine preparations.

tions, and studies of the platelets, show no deviation from the normal other than is to be expected in a very mild, slowly developing secondary anæmia incident to an acute infection. In the three cases in which it was possible to follow the blood picture for a long period the pathological lymphoid cells were found present for some weeks after the disappearance of other signs and symptoms, but eventually the blood returned to normal. It was at this stage that Case VI, diagnosed largely from the history and data afforded by her physician in a distant state, first came under observation here.

There is nothing distinctive in the changes in the lymph glands beyond a rather definite hyperplasia of the lymphoid cells. The sections from the three cases examined are quite similar, with minor variations due to the difference in the stage of the disease when the glands were excised. It will be seen that the reports from the several pathologists agree closely. There is no indication of Hodgkin's Disease, tuberculosis, or lymphosarcoma, and no definite histological distinction can be made between the glands in this group and in lymphatic leukæmia save in the degree of hyperplasia.

The frequency of pharyngitis and slight tonsillitis and the early enlargement of the cervical nodes point toward the respiratory tract as the atrium of infection. The sequence of events, which can be followed especially well in the first case, is interesting. With the onset of the symptoms of infection there may be a slight leucopenia. Then come the swelling of the lymph glands and the gradually increasing lymphocytosis and enlargement of the spleen. The height of the lymphocytosis and of the glandular and splenic enlargement may be reached at the end of the febrile period and these features persist to a certain extent for weeks after the patient is symptomatically well. The suggestion is obvious that the poison causing the disease produces first a slight damage to the blood-forming organs followed by evidences of stimulation of the lymphoid elements which continues for some time after the intoxication has apparently ceased. A phenomenon somewhat similar in kind but less in degree is seen in the leucopenia of typhoid and some other fevers followed by a post-infectious lymphocytosis.

One question naturally arises in this group of cases as well as in the leukæmias. Is the peculiar reaction due to any special quality in the exciting agent of the disease or is it referable to a definite tendency on the part of the reacting individual? Our data do not furnish a categorical reply to this question, but there is one interesting observation in the first case which may perhaps be accepted as bearing upon this point. Nine weeks after the temperature became normal the patient suffered from a typical attack of follicular tonsillitis with the usual polymorphonuclear leucocytosis. The count which preceded this one was made 11 days before and showed 52 per cent mononuclears in a total white count of 8700. This one observation would seem to indicate that there was no constant peculiarity in this individual's reaction to ordinary acute infections.

The differentiation from a beginning lymphatic leukæmia may be difficult. Fever, malaise and evidences of upper respiratory tract infection are more or less characteristic of acute leukæmia. In that disease, however, with a low general leucocyte count one is apt to find a more marked anæmia, a tendency to hemorrhage, and many fragile cells with their resultant "smudges" in the blood smears. The cells which are not fragile are usually normal in appearance or, if not normal, are all of the same variety, while in the cases of infectious mononucleosis there is a diversity of types (see plates). The benign course with the early disappearance of fever and more gradual return of the blood picture to normal is the safest criterion and indeed the only one of any value in some of the reported cases which resemble leukæmia even more closely than those of this report. So close has been this resemblance in certain instances that eminent hematologists have considered the possibility of a leukæmia of transient nature from which the patient recovers spontaneously.

The differentiation from Hodgkin's Disease presents less difficulty. The blood picture is not strongly suggestive of that affection, the lymphatic enlargement is general rather than regional as is commonly seen in Hodgkin's Disease, and the histology of the excised gland does not suggest this diagnosis.

SUMMARY

The six cases presented in this paper exhibited a mononuclear leucocytosis in reaction to acute infection. The symptoms and signs in all are so nearly the same that they apparently constitute a distinct clinical syndrome. Each case ran a febrile course with moderately severe prostration. In four there were evidences of a tonsillitis or other infection of the upper respiratory tract, and a moderate general glandular enlargement. Four of the cases had, in addition, a palpable spleen. The total leucocyte count was normal at first, but later became moderately increased. The differential formula showed a slight increase in the cells of the large mononuclear-transitional group and the presence of many pathological lymphoid forms. Later there was a leucocytosis which was largely due to an increase in lymphoid cells among which were many pathological forms.

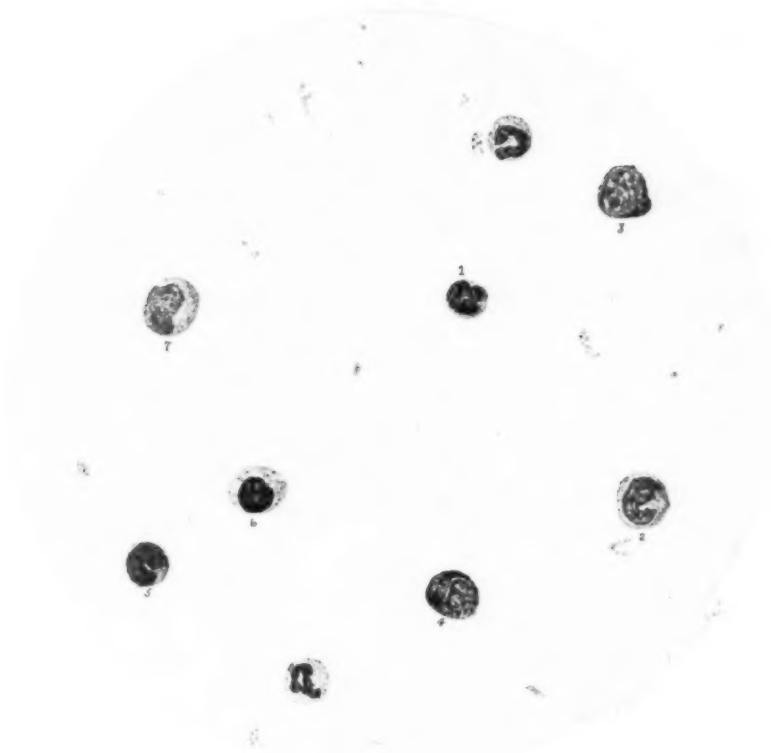
From a study of these cases no evidence has been adduced that they are dependent upon a single etiological factor. The data afforded by Case I, which showed a polymorphonuclear leucocytosis in reaction to an acute tonsillitis one year after the mononuclear leucocytosis, would suggest that this reaction is due to the character or peculiar action of the infecting organism rather than to a constant peculiarity of reaction in the infected individual.

The information obtained from a study of these cases permits the following conclusions:

1. In addition to the mononuclear leucocytosis seen commonly in children one may encounter occasionally a mononuclear leucocytosis in adults in reaction to acute infection.

2. The mononuclear leucocytosis in adults in reaction to acute infection is not a simple lymphocytosis, as in children, but is made up largely of pathological forms, probably all lymphoid in origin.

3. Among the cases in adults presenting a mononuclear leucocytosis of this type there occurs a group with symptoms



COMPOSITE BLOOD FIELD DRAWN TO SHOW SOME TYPES OF LARGE MONONUCLEAR CELLS ENCOUNTERED IN THE MONONUCLEOSES OF AN ACUTE INFECTION.

(1) Small lymphocyte.
(2) Cell of large mononuclear-transitional group.
(3), (4), (5) Cell forms commonly seen in infectious mononucleoses, but rarely, if ever, in normal blood.
(6) Large lymphocyte commonly seen in normal blood.
(7) Large lymphocyte occasionally seen in normal blood.
Wilson's modification of Romanowsky stain.

and signs so much alike that they may be considered provisionally as a clinical entity.

4. When first seen during the febrile period, especially in the early stages, these cases cannot be differentiated with assurance from leukæmia; but the subsequent course makes the diagnosis clear.

5. The prognosis, so far as may be judged from a series of six cases, is good.

BIBLIOGRAPHY

1. Türk (Quoted from A. Herz): Die akute Leukämie. Leipzig u. Wien, 1911, p. 159.

2. Lüdke (Quoted from A. Herz). Die akute Leukämie. Leipzig u. Wein, 1911, p. 161.

3. Marchand, Fritz: Ueber ungewöhnlich starke Lymphocytose im Anschluss an Infectionen. Deutsches Arch. f. klin. Med., Leipz., 1913, CX, 359.

4. Cabot, R. C.: The lymphocytosis of infection. Am. J. M. Sc., Phila., 1913, CXLV, 335.

5. Sanders, M. E.: The nature of the lymphocytosis of acute infections. J. Lab. & Clin. M., St. Louis, 1919, IV, 344.

6. Evans, F. A.: Experimental Study of the Mononuclear Cells of the Blood and Tissues. Arch. Int. Med., Chicago, 1916, XIII, 692.

7. Graham, G. S.: The Oxidizing Ferment of the Myelocytic Series of Cells and Its Demonstration by the Alphanaphthol-Pyronin Method. J. Med. Research, Boston, 1916-1917, XXXV, 235.

PNEUMOCOCCUS TYPE I VEGETATIVE ENDOCARDITIS

REPORT OF A CASE FOLLOWING AN ATTACK OF LOBAR PNEUMONIA

By HENRY M. THOMAS, JR., M. D., Resident Physician, AND DWIGHT O'HARA, M. D., Assistant Resident Physician

(From the Pneumonia Service of the Boston City Hospital.)

The case described in this report is of singular interest owing to its unusual clinical course and rare pathological findings. Presenting, as it did, difficult problems as to diagnosis and treatment, we feel that it will be of interest to all clinicians.

CASE REPORT.

M. O'H., 45, white, m., metal polisher. Admitted to Hospital May 19, 1920.

Family History and *Marital History* unimportant.

Past History.—Measles, whooping cough and scarlet fever as a boy. Pleurisy in 1917, ill 10 days. Influenza 18 months ago.

Habits.—Moderate use of tobacco, whiskey and beer, three or four drinks a day.

Present Illness.—Sudden onset three days ago with pain in the right side, which was increased on deep breathing. Cough with rusty sputum. Boneaches and vomiting.

Physical Examination.—Well developed and well nourished man, lying comfortably in bed. T. 104.0°, P. 100, R. 40.

Teeth, poor. Pharynx, injected.

Lungs. Emphysematous. Signs of solidification of entire right lower lobe, and a small patch in the left lower lobe.

Heart and abdomen. Negative.

Remaining physical examination unimportant.

White blood count, 16,500.

May 20. X-ray report—Consolidation at right base and infiltration of right hilus.

May 21. (Sixth day of disease.) Report of sputum examination, Pneumococcus Type I. Report of blood culture, Pneumococcus Type I. Three doses of 100 c. c. of antipneumococcic serum, Type I, Massachusetts State Board of Health, given intravenously at eight-hour intervals, without reaction.

May 22. 4th, 5th and 6th doses of serum given, intravenously.

May 23. Temperature down to 100° (rectal) and pulse 80 per minute. The general condition seems much improved. Signs in lungs remain as on admission. Serum treatment suspended.

May 24. Temperature down to 98.6° (rectal) and pulse 75 per minute.

May 25. Temperature rose in the evening, but there were no subjective symptoms.

May 26. A diffuse urticaria developed over the extremities and body, and the temperature again reached 101° (rectal), in the evening. Physical examination reveals nothing new, and the temperature is thought to be due to serum sickness.

May 28. Serum sickness continues. Temperature 104° (rectal), this evening.

May 30. The patient seems better to-day. The lung signs are nearly as on admission, with perhaps a few more medium, moist râles in the right base behind.

June 1. The temperature remained down last night and to-day, but the patient does not seem to be improving.

June 3. For the past few days the patient's condition has not been improving, but repeated examinations fail to reveal any cause for the continued illness. There is some evidence of early resolution in the right lower lobe, and there is continued solidification in the left lower lobe. X-ray taken yesterday showed consolidation in right lung. A slight weakness on the right side of the face has been noticed, but consultation with the Neurological Service showed no definite involvement of the central nervous system. White blood count, 24,000.

June 5. A blood culture taken three days ago was reported positive for Pneumococcus Type I. Nothing new could be found to account for the septicæmia, but in view of the recent article by Blake and Cecil, in which they report observing pneumococcus septicæmia in monkeys for days after the crisis had occurred. it was decided to continue the intravenous treatment. For this purpose Mulford's Type I Antipneumococcus Antibody Extract was employed, in order to avoid anaphylactic shock from the use of horse serum, to which the patient was unquestionably sensitized by that time. Two doses of 100 c. c. were given intravenously without reaction.

June 6. 100 cc. Antibody Extract administered intravenously.

June 7. Following the treatment two days ago the temperature remained lower and the patient seemed somewhat improved, but yesterday afternoon he had a chill, after which his temperature rose to 104°. As our supply of Mulford's Antibody Extract was very small, it was decided to desensitize the patient for horse serum and to recommence intravenous serum therapy. The reason for this decision was that we hoped to combat the focus of infection, whatever it might be. Desensitization progressed rapidly without reaction until 10 c. c. were given intravenously.

This dose brought on a typical, mild anaphylactic reaction, which was controlled by adrenalin and atropine hypodermically. After this, 10 c. c., 15 c. c., 25 c. c. and 40 c. c. were given at hourly intervals without reactions.

June 9. Serum treatment continued yesterday and to-day. The patient's condition continues to become worse. A blood culture taken yesterday shows 3000 colonies per cc. of blood. The ears are negative. Neurological examination negative except for weakness of right facial muscles. The urine has been found negative repeatedly. An X-ray, taken June 7, suggested the possibility of a lung abscess in the middle of the right lung. At the angle of the right scapula the breath sounds have a somewhat amphoric quality, with medium to large consonating râles. The

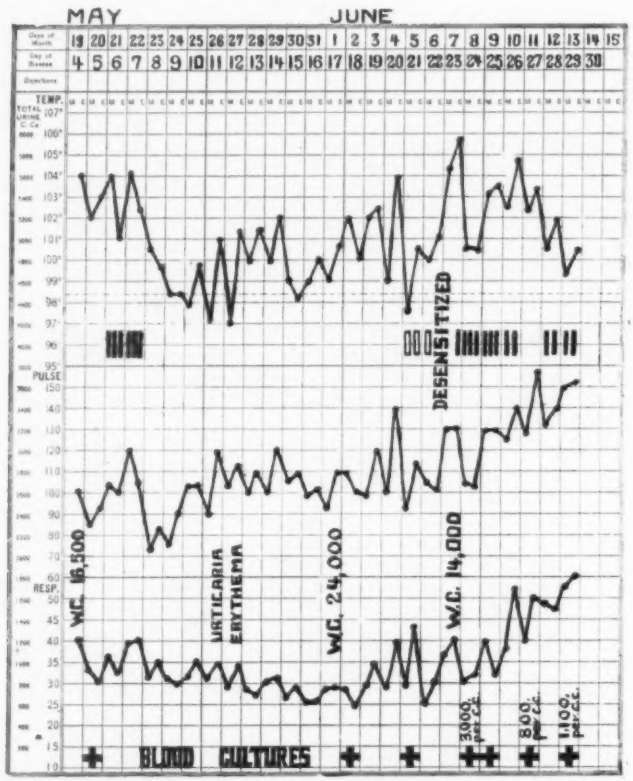


CHART I.—Clinical chart giving temperature, pulse, and respiration and indicating the points at which blood cultures were taken and serum treatments administered.
■ Indicates 100 c. c. of Antipneumococcus Type I horse serum.
□ Indicates 100 c. c. of Mulford's Type Antipneumococcus antibody extract.

persisting signs at both bases and the bacteræmia are the only positive findings. There is no evidence of pericardial involvement, either by physical or by X-ray examination. In view of the fact that the original attack of pneumonia was apparently recovered from, the lung condition does not seem an adequate explanation for the septicæmia. In spite of the total absence of cardiac murmurs at any time throughout the course of the disease, an acute endocarditis may exist and be responsible for the present clinical picture.

June 11. As no apparent benefit has been derived from serum treatment at this stage of the illness, it is decided to modify the method of administration from three intravenous doses a day to one intravenous and one subcutaneous dose. Although little hope of benefit from serum is entertained, it is the only rational method of treatment that occurs to us. The patient's condition continues to become worse. His only complaints are of extreme thirst and dryness of the mouth and throat. He takes fluids in large amounts and is given 4 ounces of whiskey a day.

June 13. Signs of solidification are more marked in both bases. To-day there is weakness of the left arm. The general condition is much weaker, and the terminal event seems a matter of hours. The septicæmia continues, having fallen to 800 colonies per c. c. on June 11.

June 14. The patient died this morning at 12.30 a. m. A blood culture taken yesterday shows 1100 colonies per c. c. of blood.

Diagnosis.—Lobar pneumonia—Right lower lobe. Left lower lobe, Pneumococcus Type I. Septicæmia, Pneumococcus Type I. Acute endocarditis (?). Lung abscess, right lower lobe (?). Brain Abscess (?).

Autopsy Findings.—At the post-mortem examination the following conditions were disclosed:

Lobar pneumonia of the left and right lower lobes, and the lower portion of the right upper lobe. Abscess of the right lower lobe, 4 x 3 x 2 cm. Hemorrhagic infarct of left upper lobe (small). Right and left healed pleurisy. Acute vegetative endocarditis of tricuspid valve. Focal meningitis. Chronic aortitis and arteriosclerosis. Acute splenic tumor.

The points of interest in the pathological findings of this case are several.

1. There was no gross evidence of resolution in any of the solidified areas of the lung tissue.

2. The endocarditis was limited to the tricuspid valve and had given rise at this point to a large vegetative mass (see Fig. 1), 4 x 3 x 1.5 cm., consisting of yellowish-grey, slightly friable tissue, over the surface of which there were small pinpoint reddish areas. Microscopically the vegetation was composed of masses of fibrin and cellular debris enclosing collections of gram-positive diplococci (see Fig. 2). The rest of the endocardium was free from acute lesions, nor was there any chronic endocarditis.

A few plaques of arterio-sclerosis were scattered over the mitral and aortic cusps.

3. The meningitis was localized to an area about 2.5 x 2 cm., near Broca's area on the antero-lateral aspect of the left hemisphere, consisting of greenish purulent material lying beneath the arachnoid but not extending into the brain tissue or displacing it. Smears from the pus showed gram-positive diplococci.

DISCUSSION.

Endocarditis complicating pneumonia has long been recognized. Endocarditis caused by the pneumococcus was discussed by Netter, who in 1886 published a comprehensive review of the literature to that date, including 82 cases. He also reported the results of experiments whereby he was able to produce endocarditis by the intravenous injection of pneumococci, especially after the endocardium had been previously traumatised. He emphasized the point that the pneumococcus involves the right heart one-sixth times as often as the left, whereas other organisms involve the right heart only one-nineteenth times as often as the left. He also confirmed the observation of Heschl that endocarditis following pneumonia is frequently found associated with meningitis.

FIG. 1.—Photograph of the right heart showing the large polypoid vegetation on the tricuspid valve.

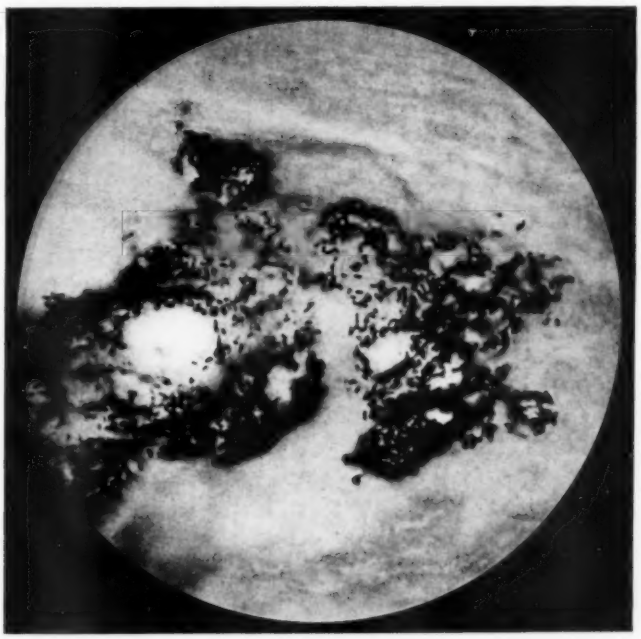


FIG. 2.—Photomicrograph of a section taken from the edge of the vegetation, showing gram-positive diplococci. (× 1000.)

Osler, in 1885, reported the autopsy findings in 209 acute ulcerative endocarditis cases, 54 of which were in pneumonia patients.

Weichselbaum, in 1888, published a report of an extensive investigation of the pathological anatomy of endocarditis. He reported 29 cases, of which 6 were due to the pneumococcus, as well as describing the lesions produced experimentally in laboratory animals.

In 1890 Debove reported a case of tricuspid endocarditis of pneumococcus origin, emphasizing the absence of physical signs and offering as an explanation for the site of the lesion the lowered resistance of the right heart in pneumonia due to prolonged overwork.

In 1898 James reported two fatal cases of pneumococcus endocarditis in which neither of the patients had suffered from any pulmonary involvement.

In 1902 Wells reviewed the literature and pointed out the fact that acute endocarditis may occur early in the course of the disease (seventh day in one case and ninth day in another). He also stated that recovery from pneumococcus endocarditis was likely to lead to unimpaired function of the valve owing to the slight tendency shown by this type of lesion to the formation of cicatricial contraction.

Preble, in 1904, added 50 cases from the literature to the 82 previously reported by Netter and carefully analyzed the 132 cases. Little of note has been added to the subject since that time. Among his conclusions he stated that endocarditis complicates 1 per cent of all cases of pneumonia and about 5 per cent of the fatal cases. Infarcts occur in about half of the cases. Pneumococcus endocarditis is about twice as common relatively in males as in females. Physical signs of the endocarditis are often entirely lacking. One of Preble's personal cases was the only one, confirmed by a positive blood culture, that recovered, but he thought it probable that a higher percentage of recoveries occur than the reports so far published would lead one to infer.

Of 141 pneumococcus endocarditis cases collected by Preble in which the site of the lesion was indicated, 12, or 8.5 per cent, involved the tricuspid valve alone, whereas 56 and 40 involved the aortic and mitral valves respectively. A careful study of the literature since that time serves only to add five more cases where the lesion was confined to the tricuspid valve; Hawkins two in 1907, Romback one in 1911, and Menétrier two in 1919. With the case reported in this paper that brings the total to 18 cases.

Few cases of pneumococcus endocarditis have been reported since the division of the pneumococcus into its subgroups. In a series of 11 Type I pneumonia cases treated with antipneumococcus serum reported by Bloomfield in 1917, one developed acute vegetative endocarditis of the mitral valve.

Mildred Clough, in an analysis of the complications of a series of 36 pneumonia cases, found two instances of acute endocarditis; one caused by a Type III and one by a Type IV pneumococcus. Palmer, in 1919, reported two casses of acute pneumococcus endocarditis of the mitral valve, both caused by the Type I organism. Wadsworth, in 1918, reported pneumococcus endocarditis occurring in horses which were being immunized against living pneumococci. In eight autopsies performed on horses dying during the process of immunization, seven showed lesions of acute endocarditis, five due to a Type I pneumococcus and one each to a Type II and Type III pneumococcus. He stated that the lesions caused by the different type organisms were identical, but it would seem that the preponderance of Type I cases is significant.

In addition to this small group of reported cases there are certain facts which make it seem quite possible that the Type I pneumococcus is responsible for the majority of pneumococcus endocarditis cases, although the proof lies in the accumulation of much more data. In the first place out of 31 cases of pneumococcus empyema, 20, or 60 per cent, were caused by Type I pneumococcus. Out of 49 positive blood cultures 18 were Type I. Of the three infected joints occurring on this service, two were caused by Type I pneumococcus and the other by Type IV pneumococcus. The only case complicated by meningitis was caused by Type I pneumococcus. These facts show the tendency the Type I pneumococcus has to cause secondary infections or complications and to invade the blood stream. In the second place morphologically and culturally Type I pneumococcus is frequently indistinguishable from a streptococcus viridans, which is considered the most common cause of endocarditis. That this cultural likeness is of any importance remains to be shown.

This case suggests the advisability of frequent and early blood cultures during the convalescence from pneumonia whenever a rise in temperature occurs. In a case treated with serum a possible serum sickness should not lead one to neglect this measure, as active serum treatment, while not very promising, is the only procedure at present available with which to combat this condition.

SUMMARY.

An unusual case of Type I pneumococcus endocarditis, namely, of the tricuspid valve, is reported. This case brings up several interesting points upon which more statistical data are needed before positive statements can be made. There is, however, some cause for believing that pneumococcus endocarditis is usually caused by the Type I pneumococcus.

NOTE: We wish to express our gratitude to Dr. F. B. Mallory for his co-operation in this report and also to Miss Lillian M. Leavitt for the technical work of preparing the microscopic sections and making the photographs.

BIBLIOGRAPHY.

1. Blake, F. G., and Cecil, R. L.: J. Exp. Med., XXXI, 403.
2. Netter: Arch. physiologie normale et pathologique, 1886, VIII, 106.
3. Heschl: Oesterr. Ztschr. f. prakt. Heilk., Wien, 1862, VIII, 217.
4. Osler, Wm.: Gulstonian Lecture, No. III, 1885.
5. Weichselbaum, A.: Ziegler's Beiträge, 1888, IV, 127.
6. Debove: Gazette des hôpitaux, 1890, LXIII, 606.
7. James, W. B.: Presbyterian Hosp. Reports, N. Y., 1898, III, 325.

8. Wells, E. F.: J. Am. Med. Ass., 1902, XXXIX, 978.
9. Preble, H. B.: Am. J. of Med. Sc., 1904, CXXVIII, 782.
10. Hawkins, F. H.: Tr. Clin. Soc., London, 1907, XL, 55.
11. Romback, K. A.: Nederl. Tidjschr v. Geneisk., Amsterdam, 1911, II, 305.
12. Menétrier, P.: Bull. et mém. Soc. méd d. hôp. de Par., 1919, 3me S., XLIII, 679.
13. Bloomfield, A.: Johns Hopkins Hospital Bulletin, 1917, XXVIII, 301.
14. Clough, M. C.: Johns Hopkins Hospital Bulletin, 1917, XXVIII, 306.
15. Palmer, W. W.: Medical Clinics of North America, 1919, II, No. 4, 987.
16. Wadsworth, A. B.: Jour. Med. Research, 1918-19, XXXIX, 279.

NOTES ON NEW BOOKS

Parasites and Parasitosis of the Domestic Animals. By B. M Underhill, V. M. D. (*New York, 1920, The MacMillan Company.*)

This book is not an exhaustive treatise on zoölogy, nor is it intended to be. As the author states in his preface, he has "aimed to present clearly, concisely and in an orderly manner such matter pertaining to the subject at hand as seems most essential to the needs of the student and practitioner." This aim the author has accomplished. The commoner animal parasites and the diseases caused by them in domestic animals are discussed adequately. To the description of most of the diseases there is added a brief note on treatment and suggestions as to their prevention. The illustrations are numerous and clear. Many of them are schematic. This book will be a success as a text-book. In addition to this, because of the interesting way in which the subject matter is presented, it can be recommended as not only profitable but also pleasant reading for any physician, and even probably for laymen interested in domestic animals.

F. A. E.

A Laboratory Syllabus of Clinical Pathology. By Charles E. Simon. Cloth $2. (*Lea and Febiger, Philadelphia and New York.*)

The author states that the object of this book is to eliminate waste motion in teaching the laboratory side of diagnosis and thus lighten an already overburdened medical curriculum without curtailing the attention given to this important and ever-growing subject. The need for some such measure is acutely felt by everyone with responsibilities similar to those of Dr. Simon, and this guide to his methods from such an experienced teacher in this subject is sure to be appreciated. The subjects for study are wisely chosen and the field is well covered. Many subjects, however, are so briefly presented that one is inclined to question seriously if in actual teaching a sufficient insight would be obtained by the student in the time allotted to them in this syllabus. For example, it would appear impossible to teach the student routine qualitative and quantitative examination of the urine in two two-hour laboratory periods, and microscopical examination in one similar period. One two-hour laboratory period for study of the blood pictures presented by all types of leukemia, and another for all types of anemia are certainly inadequate. Such considerations as these raise the question as to whether a teacher in following this syllabus would succeed in saving time without curtailing the attention given by the student to this fundamental subject. To some who have no more time allotted to them than is outlined in this syllabus it would probably seem wiser to present some parts more fully, rather than cover so much ground thus hastily. The time given to any individual subject, however, may be increased, as Dr. Simon suggests, according to the judgment of the teacher. If this liberty is taken with it, the book will surely afford an outline to follow for those undertaking the teaching of this branch for the first time and as such will be of great value.

F. A. E.

Infectious Diseases. Practical Text-Book. By Claude Buchanan Ker. Cloth $7. (*London, Oxford University Press, 1920.*)

From the standpoint of text-books no branch of medicine has been dealt with more inadequately than the infectious diseases. It is a pleasure, therefore, to find a concise and yet sufficiently comprehensive treatise such as that of Dr. Ker. Without going into great detail, or inflicting upon the reader large statistical compilations, the writer presents excellent and vivid clinical descriptions of the various diseases, emphasized by a sufficient number of very satisfactory illustrations.

The book is thoroughly up-to-date, and in the section on etiology prevailing views as to the causes of the various infectious diseases are discussed in a conservative and critical manner.

The sections on treatment are excellent, the questions of diphtheria antitoxin and meningitis serum being handled especially well.

The first and last chapters, dealing respectively with the general questions of infectious diseases and with fever hospital problems, serve to round out the book.

A. L. B.

Epidemic Encephalitis. By Frederick Tilney and Hubert S. Howe. Cloth $3.50. (*New York: Paul B. Hoeber, 1920.*)

The book is divided into two parts. Part I (76 pages) reproduces verbatim the article "Epidemic Encephalitis—A preliminary consideration of some of its prominent clinical and pathological manifestations," by Tilney and Riley in the Neurological Bulletin, Vol. II, No. 3, page 106. This article presents 20 cases illustrating the different clinical types of this disease.

Part II is entitled "Studies of selected cases," and is devoted, in 171 pages, to a presentation of 11 cases, one of which has appeared in a previous publication (Neurological Bulletin, Vol II, No. 5, page 190). The etiology, pathology, symptoms, laboratory findings, etc., are briefly discussed. The bulk of the book is taken up by detailed case reports which could be greatly abbreviated by the elimination of many negative data. The photographs and photomicrographs are splendidly reproduced.

W. M. H.

THE JOHNS HOPKINS HOSPITAL BULLETIN

It is issued monthly. Volume XXXI is in progress. The subscription price is $3.00 per year. (Foreign postage, 50 cents.) Price of cloth-bound volumes, $3.50 each.

A complete index to Vols. I-XVI of the Bulletin has been issued. Price, 50 cents, bound in cloth.

Orders should be addressed to

The Johns Hopkins Press, Baltimore, Md.

BOOKS RECEIVED

The Medical Clinics of North America. Volume 3, Number 3, November, 1919. Mayo Clinic Number. 8°. 551-847. W. B. Saunders Company, Philadelphia and London.

Chicago. Report and Handbook of the Department of Health of the City of Chicago for the Years 1911 to 1918 Inclusive. John Dill Robertson, M. D., Commissioner of Health. 1919. 8°. 1535 pages. Chicago.

The After-Treatment of Surgical Patients. By Willard Bartlett, A. M., M. D., F. A. C. S. and Collaborators. Vol. 1. With two hundred twenty-two original illustrations and one color plate. Vol. 2. With two hundred thirteen original illustrations. 1920. 8°. 1066 pages. C. V. Mosby Company, St. Louis.

The American Illustrated Medical Dictionary. A New and Complete Dictionary of the Terms Used in Medicine, Surgery, Dentistry, Pharmacy, Chemistry, Nursing, Veterinary Science, Biology, Medical Biography, etc. By W. A. Newman Dorland, A. M., M. D., F. A. C. S. Tenth edition, revised and enlarged. 1920. 8°. 1201 pages. W. B. Saunders Company, Philadelphia and London.

Johns Hopkins University and Hospital. Researches in Urology. Collected reprints from The Brady Urological Institute. Vol. I. Kidney, Ureter, Bladder. Vol. II, Prostate, Urethra, Miscellaneous. 1919. 4°. Baltimore.

United States, Public Health Service. Annual Report of the Surgeon General of the Public Health Service of the United States for the Fiscal Year 1919. 8°. 346 pages. Government Printing Office, Washington.

United States, War Department. Annual Report of the Surgeon-General U. S. Army to the Secretary of War. Two volumes. 1919. 8°. 2167 pages. Government Printing Office, Washington.

Sydney. Calendar of the University of Sydney for the Year 1919. 8°. 736 pages. Angus and Robertson, Ltd. Sydney.

United States, War Department. Physical Examination of the First Million Draft Recruits: Methods and Results. Compiled under direction of the Surgeon General. Bulletin No. II. 1919. 8°. 521 pages. Government Printing Office, Washington.

Defects Found in Drafted Men. Statistical Information Compiled from the Draft Records. Showing the Physical Condition of the Men Registered and Examined in Pursuance of the Requirements of the Selective Service Act. Prepared under the direction of the Surgeon General M. W. Ireland. By Albert G. Love, M. D., and Charles B. Davenport. Printed for the use of the Senate Committee on Military Affairs. 1919. 8°. 359 pages. Government Printing Office, Washington.

United States, Council of National Defense, Reconstruction Research Division. Readjustment and Reconstruction Information. I. Readjustment and Reconstruction Activities in Foreign Countries. 1919. 8°. 188 pages. Washington.

Aphasia and Associated Speech Problems. By Michael Osnato, M. D. Preface by Frederick Tilney, M. D., Ph. D. 1920. 12°. 191 pages. Paul B. Hoeber, New York.

Education in War and Peace. By Stewart Paton, M.D. 1920. 12°. 106 pages. Paul B. Hoeber, New York.

Rambling Recollections. An autobiography. By A. D. Rockwell, M. D. 1920. 8°. 332 pages. Paul B. Hoeber, New York.

Physical Reconstruction and Orthopedics. By Harry Eaton Stewart, M. D. Authorized for Publication by the Surgeon General of the U. S. Army. Sixty-seven original illustrations and two diagrams. 1920. 8°. 240 pages. Paul B. Hoeber, New York.

Injuries to the Head and Neck. By H. Lawson Whale. With preface by Colonel Frederick F. Burghard, C. B., M. D., M. S., F. R. C. S [1919.] 8°. 322 pages. Paul B. Hoeber, New York.

Common Diseases of the Skin. With Notes on Diagnosis and Treatment. By G. Gordon Campbell, B. Sc., M. D., C. M. 1920. 8°. 229 pages. Macmillan Company, New York.

The Life of Leonard Wood. By John G. Holme, Illustrations from photographs. 1920. 12°. 228 pages. Doubleday, Page & Co., Garden City, New York.

Medical Society of London. Transactions. Volume the Forty-second. Edited by Edmund Cautley, M. D., and Donald Armour, C. M. G., F. R. C. S. 1919 8°. 253 pages. Harrison & Sons, London.

The Physiology of Muscular Exercise. By F. A. Bainbridge M. A., M. D. Cantab., D. Sc., F. R. C. P., F. R. S. With 22 diagrams. 1919. 8°. 215 pages. Longmans, Green & Co., London and New York.

Principles and Practice of Physical Diagnosis. By John C. DaCosta, Jr., M. D. Fourth edition, thoroughly revised. 1919. 8°. 602 pages. W. B. Saunders Company, Philadelphia and London.

Laboratory Manual of Pharmacology Including Materia Medica, Pharmacopedics and Pharmacodynamics. By A. D. Bush, B. Sc., M. D. Illustrated with full-page plates, many in colors. 1919. 4°. 251 pages. F. A. Davis Company, Philadelphia.

The Diseases of Infants and Children. By J. P. Crozer Griffith, M. D., Ph. D. With 436 illustrations including 20 plates in colors. 1919. 8°. Volume I, 885 pages. Volume II, 657 pages. W. B. Saunders Company, Philadelphia and London.

A Laboratory Manual of Physiological Chemistry. By Elbert W. Rockwood, M. D., Ph. D. Fourth edition, revised and enlarged, illustrated with one colored plate, three plates of microscopic preparations and seventeen engravings. 1919. 12°. 316 pages. F. A. Davis Company, Philadelphia.

American Academy of Ophthalmology and Oto-Laryngology. Transactions of the Twenty-fourth Annual Meeting, 1919. 8°. 474 pages.

George Williams Hooper Foundation for Medical Research. Collected Reprints. The Department of Research Medicine of the University of California Medical School, San Francisco. Volume IV, 1918-1919. 8°.

American Surgical Association. Transactions. Volume the Thirty-seventh. Edited by John H. Jopson, M. D. 1919. 8°. 519 pages. Printed for the Association. Philadelphia.

American Gynecological Society. Transactions. Volume 44 for the year 1919. Edited by George Gray Ward, Jr., M. D. 1919. 8°. 389 pages. Philadelphia.

Surgical Shock and the Shockless Operation Through Anoci-Association. By George W. Crile, M. D., and William E. Lower, M. D. Second edition of "*Anoci-Association*" thoroughly revised and rewritten. Edited by Amy F. Rowland, B. S., 1920. 8°. 272 pages. W. B. Saunders Company, Philadelphia and London.

Pasteur, The History of a Mind. By Emile Duclaux. Translated by Erwin F. Smith and Florence Hedges. Illustrated. 1920. 8°. 363 pages. W. B. Saunders Company, Philadelphia and London.

Diseases of the Chest and the Principles of Physical Diagnosis. By George William Norris, A. B., M. D., and Henry R. M. Landis, A. B., M. D. With a chapter on the Electrocardiograph in Heart Disease. By Edward B. Krumbhaar, Ph. D., M. D. Second edition, revised. 1920. 8°. 844 pages. W. B. Saunders Company, Philadelphia and London.

A Text-Book of Physiology. For Students and Practitioners of Medicine. By Russell Burton-Opitz, S. M., M. D., Ph. D. Illustrated. 1920. 8°. 1185 pages. W. B. Saunders Company, Philadelphia and London.

The Nation's Food. A Statistical Study of a Physiological and Social Problem. By Raymond Pearl, Ph. D., Sc. D., LL. D. 1920. 8°. 274 pages. W. B. Saunders Company, Philadelphia and London.

Sexual Impotence. By Victor G. Vecki, M. D. Sixth edition, revised. 1920. 8°. 424 pages. W. B. Saunders Company, Philadelphia and London.

Orthopedic and Reconstruction Surgery. Industrial and Civilian. By Fred. H. Albee, A. B., M. D., Sc. D., F. A. C. S. With 804 illustrations. 1919. 8°. 1138 pages. W. B. Saunders Company, Philadelphia and London.

The Principles of Anatomy, as Seen in the Hand. By Frederic Wood Jones, D. Sc., M. B., B. S. Lond. With two plates and 123 text figures. 1920. 8°. 325 pages. P. Blakiston's Son & Co., Philadelphia.

New Jersey State Department of Health. Forty-Second Annual Report of the Department of Health of the State of New Jersey. 1919. 8°. 440 pages. 1920. Published by the State. Trenton, N. J.

Central Indiana Hospital for the Insane. Report from the Department of Pathology and the Department of Clinical Psychiatry, Central Indiana Hospital for the Insane, 1915-1916 and 1916-1917. Volume VII. 1919. 8°. 684 pages. Wm. B. Burford (Indianapolis).

University of Illinois. College of Medicine, Chicago. Collected Studies from the Department of Pathology and Bacteriology. Volume IV, 1918-1919.

Association of American Physicians. Transactions of the Thirty-fourth Session. Volume XXXIV, 1919. 8°. 378 pages. Printed for the Association, Philadelphia.

A Study of Experimental Meningitis. A series of Papers from the Army Neuro-Surgical Laboratory. By Louis H. Weed, Paul Wegeforth, James B. Ayer and Lloyd D. Felton. Monograph No. 12. 1920. 8°. 145 pages. The Rockefeller Institute for Medical Research, New York.

Leonard Wood on National Issues. The Many-Sided Mind of a Great Executive Shown by His Public Utterances. Compiled by Evan J. David. With a Foreword by Edward S. Van Zile. 1920. 12°. 140 pages. Doubleday, Page & Co., Garden City, New York.

Personal Beauty and Racial Betterment. By Knight Dunlap. 1920. 12°. 95 pages. C. V. Mosby Company, St. Louis.

Handbook of Diseases of the Rectum. By Louis J. Hirschman, M. D., F. A. C. S. With two hundred and twenty-three illustrations, mostly original, and four colored plates. Third edition, revised and rewritten. 1920. 8°. 378 pages. C. V. Mosby Company, St. Louis.

"L.-P." The Treatment of Inflammation and Sepsis by Lipoid-Paraffin Dressings. By A. White Robertson. 1919. 8°. 83 pages. George Routledge & Sons, Ltd., London.

Sex Attraction. A Lecture given at the Michigan State Normal School, July, 1919. By Victor C. Vaughan, M. D., LL. D. 1920. 16°. 44 pages. C. V. Mosby Company, St. Louis.

General and Dental Pathology. With Special Reference to Etiology and Pathological Anatomy. By Julio Endelman, M. S., D. D. S., and A. F. Wagner, A. M., M. D. With 440 illustrations, of which 340 in the section on dental pathology are original, and four colored plates. 1920. 8°. 593 pages. C. V. Mosby Company, St. Louis.

Arteriosclerosis and Hypertension. With Chapters on Blood Pressure. By Louis Warfield, A. B., M. D. (Johns Hopkins), F. A. C. P. Third edition. 1920. 8°. 265 pages. C. V. Mosby Company, St. Louis.

Traité de l'Immunité dans les Maladies Infectieuse. Par le Dr. Jules Bordet. 1920. 8°. 720 pages. Masson et Cie, Paris.

Le Sympathique et les Systèmes Associés. Anatomie Clinique, Semiologie et Pathologie Générale du Systéme Neuro-Glandulaire de la vie Organique. Par A. C. Guillaume. Préface du Dr. Pierre Marie. 1920. 12°. 160 pages. Masson et Cie, Paris.

Collected Studies on the Pathology of War Gas Poisoning. From the Department of Pathology and Bacteriology Medical Science Section Chemical Warfare Service. Under the Direction of M. C. Winternitz, Major, M. C., U. S. A. Published with the Consent of the Surgeon General U. S. Army, and the Director Chemical Warfare Service. 1920. Fol. 165 pages. Yale University Press, New Haven; Oxford University Press, London.

A Text-Book of Dermatology. By J. Darier. Authorized Translation from the Second French Edition. Edited with notes by S. Pollitzer. Illustrated with 204 engravings and 4 colored plates. 1920. 8°. 769 pages. Lea & Febiger, Philadelphia and New York.

Symptoms in the Diagnosis of Disease. By Hobart Amory Hare, M. D., B. Sc. Eighth edition, thoroughly revised. Illustrated with 195 engravings and 9 plates. 1920. 8°. 562 pages. Lea & Febiger, Philadelphia and New York.

A Diabetic Manual. For the Mutual Use of Doctor and Patient. By Elliott P. Joslin, M. D. Illustrated. Second edition, thoroughly revised. 1919. 12°. 191 pages. Lea & Febiger, Philadelphia and New York.

A Laboratory Syllabus of Clinical Pathology. By Charles E. Simon, B. A., M. D. 1919. 8°. 86 pages. Lea & Febiger, Philadelphia and New York.

American Neurological Association. Transactions of the Forty-fifth Annual Meeting. 1919. 4°. 311 pages. Philadelphia.

Royal Academy of Medicine in Ireland. Transactions. Vols. XXXVI, 1918 and XXXVII, 1919. Edited by J. Alfred Scott. M. A., M. D., F. R. C. S. I. 1920. 8°. 633 pages. John Falconer, Dublin.

American Child Hygiene Association Formerly *American Association for Study and Prevention of Infant Mortality.* Transactions of the Tenth Annual Meeting. 1919. 8°. 346 pages. 1920. Albany.

Rockefeller Institute for Medical Research. Studies. Reprints. Volume XXXII, 1920. 8°. 609 pages. New York.

American Association of Genito-Urinary Surgeons. Transactions of the Thirty-first Annual Meeting. Volume XII, 1919. 8°. 415 pages. Williams & Wilkins Company, Baltimore, Maryland.

Congress of American Physicians and Surgeons. Transactions Eleventh Triennial Session. 1919. 8°. 116 pages. Published by the Congress, New Haven, Conn.

Regional Anesthesia (Victor Pauchet's Technique). By B. Sherwood-Dunn, M. D. With 224 figures in the text. 1920. 8°. 294 pages. F. A. Davis Company, Philadelphia.

Principles and Practice of Infant Feeding. By Julius H. Hess, M. D. Second revised edition, illustrated. 1919. 12°. 343 pages. F. A. Davis Company, Philadelphia.

Medical and Surgical Report of the Presbyterian Hospital in the City of New York. Volume X, 1918. 8°. 299 pages. Corlies, Macy & Company, Inc. New York.

New York Hospital Unit. Base Hospital No. 9 A. E. F. A history of the work of the New York Hospital Unit during two years of active service. Written by the Padre. 1920. 8°. 221 pages. New York.

Neurological and Other Papers. Reprinted from the Writings of John Michell Clarke, M. A., M. D., Cantab., LL. D. Bristol, F. R. C. P., Lieut.-Colonel R. A. M. C. (T. F.). 1920. 8°. 263 pages. J. W. Arrowsmith Ltd., Bristol.

The Treatment of Wounds of Lung and Pleura. Based on a study of the Mechanics and Physiology of the Thorax. Artificial Pneumothorax, Thoracentesis, Treatment of Empyema. By Professor Eugenio Morelli. Translated from the Italian by Lincoln Davis and Frederick C. Irving. 1920. 8°. 214 pages. W. M. Leonard, Boston.

Bulletin of Iowa Institutions. Under the Board of Control. Published Quarterly. Volume XXI, 1919. 8°. 233 pages. Des Moines.

Simplified Infant Feeding. With Eighty Illustrative Cases. By Roger H. Dennett, B. S., M. D. With 14 illustrations: second edition, revised and enlarged. [1920.] 8°. 385 pages. J. B. Lippincott Company, Philadelphia and London.

Parasites and Parasitosis of the Domestic Animals. The Zoology and Control of the Animal Parasites and the Pathogenesis and Treatment of Parasitic Diseases. By B. M. Underhill, V. M. D. With 180 illustrations. 1920. 8°. 379 pages. The Macmillan Company, New York.

The Faculty of the College of Physicians and Surgeons. Columbia University in the City of New York. Thirty-five Portraits. By Doris U. Jaeger. With a foreword by Samuel W. Lambert, M. D., A. B., A. M., Ph. B. 1919. Fol. Paul B. Hoeber, New York.

Advanced Lessons in Practical Physiology. For Students of Medicine. By Russell Burton-Opitz, S. M., M. D., Ph. D. Illustrated. 1920. 8°. 238 pages. W. B. Saunders Company, Philadelphia and London.

The Principles of Ante-Natal and Post-Natal Child Physiology Pure and Applied. By W. M. Feldman, M. B., B. S. (Lond.) With 6 plates and 129 illustrations. 1920. 8°. 694 pages. Longmans, Green & Co., London and New York.

Normal Histology. With Special Reference to the Structure of the Human Body. By George A. Piersol, M. D., Sc. D. 438 illustrations, 88 of which are in color. Twelfth edition. 1920. 8°. 418 pages. J. B. Lippincott Company, Philadelphia and London.

Care and Feeding of Infants and Children. A Text-Book for Trained Nurses. By Walter Reeve Ramsey, M. D. Including Suggestions on Nursing. By Margaret B. Lettice. Second edition, revised, 123 illustrations. 1920. 8°. 290 pages. Lippincott's Nursing Manuals. J. B. Lippincott Company, Philadelphia and London.

Human Parasitology. With Notes on Bacteriology, Mycology, Laboratory Diagnosis, Hematology and Serology. By Damaso Rivas, B. S. Biol., M. S., M. D., Ph. D. Illustrated. 1920. 8°. 715 pages. W. B. Saunders Company, Philadelphia and London.

The Pathology of Influenza. By M. C. Winternitz, Isabel M. Wason and Frank P. McNamara. From the Brady Laboratory of Pathology and Bacteriology, Yale University School of Medicine and the New Haven Hospital. 1920. Fol. 61 pages. Yale University Press, New Haven; Humphrey Milford. Oxford University Press, London.

PUBLICATIONS

The following nine monographs:

Benzol as a Leucotoxin. By LAURENCE SELLING, M. D. 60 pages. Price, $1.00.

Primary Carcinoma of the Liver. By M. C. WINTERNITZ, M. D. 42 pages. Price 75 cents.

The Statistical Experience Data of The Johns Hopkins Hospital, Baltimore, Md., 1892-1911. By FREDERICK L. HOFFMAN, LL.D., F.S.S. 161 pages. Price, $2.00.

Venous Thrombosis During Myocardial Insufficiency. By FRANK J. SLADEN, M. D., and MILTON C. WINTERNITZ, M. D. Price, 75 cents.

The Origin and Development of the Lymphatic System. By FLORENCE R. SABIN. 94 pages. Price, $2.00.

Leukaemia of the Fowl: Spontaneous and Experimental. By HARRY C. SCHMEISSER, M. D. Price, $2.00.

The Structure of the Normal Fibers of Purkinje in the Adult Human Heart and Their Pathological Alteration in Syphilitic Myocarditis. By O. VAN DER STRICHT and T. WINGATE TODD. Price, $2.00.

The Operative Story of Goitre. The Author's Operation. By WILLIAM S. HALSTED, M. D. Price, $3.50.

Study of Arterio-Venous Fistula with an Analysis of 447 Cases. By CURLE L. CALLANDER, M. D. Price $2.50.

are now on sale by THE JOHNS HOPKINS PRESS, Baltimore. Other monographs will appear from time to time

THE JOHNS HOPKINS HOSPITAL REPORTS

VOLUME I. 423 pages, 99 plates.

VOLUME II. 570 pages, with 28 plates and figures.

VOLUME III. 766 pages, with 69 plates and figures.

VOLUME IV. 504 pages, 33 charts and illustrations.

VOLUME V. 480 pages, with 32 charts and illustrations.

The Malarial Fevers of Baltimore. By W. S. THAYER, M. D., and J. HEWETSON, M. D.
A Study of some Fatal Cases of Malaria. By LEWELLYS F. BARKER, M. B.

Studies in Typhoid Fever.

By WILLIAM OSLER, M. D., with additional papers by G. BLUMER, M. D., SIMON FLEXNER, M. D., WALTER REED, M. D., and H. C. PARSONS, M. D.

VOLUME VI. 414 pages, with 79 plates and figures.

VOLUME VII. 537 pages with illustrations.

VOLUME VIII. 552 pages with illustrations.

VOLUME IX. 1060 pages, 66 plates and 210 other illustrations.

Contributions to the Science of Medicine.

Dedicated by his Pupils to WILLIAM HENRY WELCH, on the twenty-fifth anniversary of his Doctorate. This volume contains 38 separate papers.

VOLUME X. 516 pages, 12 plates and 25 charts.

VOLUME XI. 555 pages, with 38 charts and illustrations.

VOLUME XII. 548 pages, 12 plates and other illustrations.

VOLUME XIII. 605 pages, with 6 plates, 201 figures, and 1 colored chart.

VOLUME XIV. 632 pages, with 97 figures.

VOLUME XV. 542 pages, with 87 illustrations.

Twelve papers on pneumonia. By DRS. CHATARD, FABYAN, EMERSON, MARSHALL, MCCRAE, STEINER, HOWARD and HANES.
A Study of Diarrhœa in Children. J. H. MASON KNOX, JR., M. D., and EDWIN H. SCHORER, M. D.
Skin Transplantation. By JOHN STAIGE DAVIS, M. D.
Epidemic Cerebrospinal Meningitis and Serum Therapy at The Johns Hopkins Hospital. By FRANK J. SLADEN, M. D.

VOLUME XVI. 670 pages with 151 figures.

Studies in the Experimental Production of Tuberculosis in the Genito-Urinary Organs. By GEORGE WALKER, M. D.
The Effect on Breeding of the Removal of the Prostate Gland or of the Vesiculæ Seminales, or of Both; together with Observations on the Condition of the Testes after such Operations on White Rats. By GEORGE WALKER, M. D.
Scalping Accidents. By JOHN STAIGE DAVIS, M. D.
Obstruction of the Inferior Vena Cava with a Report of Eighteen Cases. By J. HALL PLEASANTS, M. D.
Physiological and Pharmacological Studies on Cardiac Tonicity in Mammals. By PERCIVAL DOUGLAS CAMERON, M. D.

VOLUME XVII. 586 pages with 21 plates and 136 figures.

Free Thrombi and Ball Thrombi in the Heart. By JOSEPH H. HEWITT, M. D.
Benzol as a Leucotoxin. By LAWRENCE SELLING, M. D.
Primary Carcinoma of the Liver. By MILTON C. WINTERNITZ, M. D.
The Statistical Experience Data of The Johns Hopkins Hospital, Baltimore, Md., 1892-1911. By FREDERICK L. HOFFMAN, LL. D., F. S. S.
The Origin and Development of the Lymphatic System. By FLORENCE R. SABIN, M. D.
The Nuclei Tuberis Laterales and the So-called Ganglion Opticum Basale. By EDWARD F. MALONE, M. D.
Venous Thrombosis During Myocardial Insufficiency. By FRANK J. SLADEN, M. D., and MILTON C. WINTERNITZ, M. D.
Leukæmia of the Fowl: Spontaneous and Experimental. By HARRY C. SCHMEISSER, M. D.

VOLUME XVIII. 445 pages with 124 figures.

Fasciculus I.

A Study of a Toxic Substance of the Pancreas. By E. W. GOODPASTURE, M. D., and GEORGE CLARK, M. D.
Old Age in Relation to Cell-overgrowth and Cancer. By E. W. GOODPASTURE, M. D., and G. B. WISLOCKI, M. D.
The Effect of Removal of the Spleen Upon Metabolism in Dogs; Preliminary Report. By J. H. KING, M. D.
The Effect of Removal of the Spleen Upon Blood Transfusion. By J. H. KING, M. D., B. M. BERNHEIM, M. D., and A. T. JONES, M. D.
Studies on Parathyroid Tetany. By D. WRIGHT WILSON, M. D., THORNTON STEARNS, M. D., J. H. JANNEY, JR., M. D., and MADGE DEG. THURLOW, M. D.
Some Observations on the Effect of Feeding Glands of Internal Secretion to Chicks. By M. C. WINTERNITZ, M. D.
Spontaneous and Experimental Leukæmia in the Fowl. By H. C. SCHMEISSER, M. D.
Studies on the Relation of Fowl Typhoid to Leukæmia of the Fowl. By M. C. WINTERNITZ, M. D., and H. C. SCHMEISSER, M. D.
Hyaline Degeneration of the Islands of Langerhans in Pancreatic Diabetes. By M. C. WINTERNITZ, M. D.
Generalized Miliary Tuberculosis Resulting from Extension of a Tubercular Pericarditis Into the Right Auricle. By M. C. WINTERNITZ, M. D.
Acute Suppurative Hypophysitis as a Complication of Purulent Sphenoidal Sinusitis. By T. R. BOGGS, M. D., and M. C. WINTERNITZ, M. D.
A Case of Pulmonary Moniliasis in the United States. By T. R. BOGGS, M. D., and M. C. PINCOFFS, M. D.
Gaucher's Disease (A Report of Two Cases in Infancy). By J. H. M. KNOX, M. D., H. R. WAHL, M. D., and H. C. SCHMEISSER, M. D.
A Fatal Case of Multiple Primary Carcinomata. By E. D. PLASS, M. D.
Congenital Obliteration of the Bile-ducts. By JAMES B. HOLMES, M. D.
Multiple Abscesses of the Brain in Infancy. By JAMES B. HOLMES, M. D.
Gastric Carcinoma in a Woman of Twenty-six Years. By R. G. HUSSEY, M. D.
Subdiaphragmatic Abscess with Rupture Into the Peritoneal Cavity Following Induced Pneumothorax for Pulmonary Hæmorrhage. By R. G. HUSSEY, M. D.
Heart Block Caused by Gumma of the Septum. By E. W. BRIDGEMAN, M. D., and H. C. SCHMEISSER, M. D.
Analysis of Autopsy Records.
A. The Johns Hopkins Hospital. (Table Showing Percentage of Autopsies.)
B. The City Hospitals, Bay View. (Table Showing Percentage of Autopsies.)
"The Monday Conferences."
Clinical Representatives on the Staff of the Department of Pathology.
Donation.

Fasciculus II.

The Rôle of the Autopsy in the Medicine of To-day. By M. C. WINTERNITZ, M. D.
Experimental Nephropathy in the Dog. Lesions Produced by Injection of *B. bronchisepticus* into the Renal Artery. By M. C. WINTERNITZ, M. D., and WILLIAM C. QUINBY, M. D.
Mesarteritis of the Pulmonary Artery. By M. C. WINTERNITZ, M. D., and H. C. SCHMEISSER, M. D.
A Clinical and Pathological Study of Two Cases of Miliary Tuberculosis of the Choroid. By ROBERT L. RANDOLPH, M. D., and H. C. SCHMEISSER, M. D.
The Blood-vessels of the Heart Valves. By STANHOPE BAYNE-JONES, M. D.
Equilibria in Precipitin Reactions. By STANHOPE BAYNE-JONES, M. D.
Carcinoma of the Pleura with Hypertrophic Osteoarthropathy. Report of a Case with a Description of the Histology of the Bone Lesion. By STANHOPE BAYNE-JONES, M. D.
The Interrelation of the Surviving Heart and Pancreas of the Dog in Sugar Metabolism. By ADMONT H. CLARK, M. D.
Congenital Atresia of the Esophagus with Tracheo-Esophageal Fistula Associated with Fused Kidney. A Case Report and A Summary of the Literature on Congenital Anomalies of the Esophagus. By E. D. PLASS, M. D.
Ectopia Cordis, with a Report of a Case in a Fifteen-Month-Old Infant. By JAMES B. HOLMES, M. D.
Studies in the Mechanism of Absorption from the Colon. By SAMUEL GOLDSCHMIDT, M. D., and A. B. DAYTON, M. D.
Report of Two Fatal Cases Following Percy's Low Heat Treatment of Carcinoma of the Uterus. By V. N. LEONARD, M. D., and A. B. DAYTON, M. D.
The Relationship in Typhoid Between Splenic Infarcts and Peritonitis Unassociated with Intestinal Perforation. By A. B. DAYTON, M. D.
Left Duodenal Hernia. By A. B. DAYTON, M. D.
Histological as Related to Physiological and Chemical Differences in Certain Muscles of the Cat. By H. HAYS BULLARD, M. D.
A Method of Clearing Frozen Sections. By H. HAYS BULLARD, M. D.
On the Occurrence and Significance of Fat in the Muscle Fibers of the Atrio-Ventricular System. By H. HAYS BULLARD, M. D.
Studies on the Metabolism of Cells *in vitro*. 1. The Toxicity of α-Amino-Acids for Embyonic Chicken Cells. By MONTROSE T. BURROWS, M. D., and CLARENCE A. NEYMANN, M. D.
The Significance of the Lunula of the Nail. By MONTROSE T. BURROWS, M. D.
The Oxygen Pressure Necessary for Tissue Activity. By MONTROSE T. BURROWS, M. D.
The Functional Relation of Intercellular Substances in the Body to Certain Structures in the Egg Cell and Unicellular Organisms. By MONTROSE T. BURROWS, M. D.
Studies on the Growth of Cells *in vitro*. The Cultivation of Bladder and Prostate Tumors Outside the Body. By MONTROSE T. BURROWS, M. D., J. EDWARD BURNS, M. D., and YOSHIO SUZUKI, M. D.
The Study of a Small Outbreak of Poliomyelitis in an Apartment House, Occurring in the Course of an Epidemic in a Large City. By MONTROSE T. BURROWS, M. D., and EDWARDS A. PARK, M. D.
Papilloma of the Larynx. Report of a Case Treated with Radium with Resultant Chronic Diffuse Thyroiditis. By WILLIAM C. DUFFY, M. D.
Analysis of Autopsy Records.
Autopsy Statistics.
(a) Bay View.
(b) Johns Hopkins Hospital.
Report of the Photographic Department.
General Improvements.
Donations.

VOLUME XIX. 358 pages with 29 plates.

The Structure of Normal Fibers of Purkinje in the Adult Human Heart and Their Pathological Alteration in Syphilitic Myocarditis. O. VAN DER STRICHT, M. D., and T. WINGATE TODD, M. D.
The Operative Story of Goitre, The Author's Operation. WILLIAM S. HALSTED, M. D.
Study of Arterio-Venous Fistula with an Analysis of 447 Cases. CURLE L. CALLANDER, M. D.

The set of nineteen volumes will be sold, bound in cloth, for $100.00 net. Volume II will not be sold separately. Volumes I, III, IV, V, VI, VII, VIII, X, XI, XII, XIII, XIV, XV, XVI, XVII, XVIII and XIX will be sold for $5.00, net, bound in paper, and $5.50, net, bound in cloth. Volume IX will be sold for $10.00 net.

Orders should be addressed to THE JOHNS HOPKINS PRESS, Baltimore, Md.

The Johns Hopkins Hospital Bulletins are issued monthly. They are printed by the LORD BALTIMORE PRESS, Baltimore. Subscriptions, $3.00 a year (foreign postage, 50 cents), may be addressed to the publishers, THE JOHNS HOPKINS PRESS, BALTIMORE; single copies will be sent by mail for fifty cents each. Single copies may also be procured from the BALTIMORE NEWS CO., Baltimore.